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Ministry of Health & Family Welfare

Pharmacopoeia of India

(The Indian Pharmacopoeia)

ADDENDUM (I)

TO

Third Edition
(1985)

सत्यमेव जयते

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615.19
IND-PA.I.A

PUBLISHED BY THE CONTROLLER OF PUBLICATIONS, DELHI

1989

Pharmacopoeia of India

(The Indian Pharmacopoeia)

ADDENDUM
TO
THIRD EDITIO
(1985)

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ADDENDUM (I)

To

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Notices

पुस्तकालय
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The Addendum I to the Pharmacopoeia of India 1985 amends the Indian Pharmacopoeia 1985 and constitutes a part of Indian Pharmacopoeia, Third Edition.

The General Notices and Appendices included in the Indian Pharmacopoeia 1985 and as amended in this Addendum apply both to the matter contained in the Indian Pharmacopoeia 1985 and to the matter contained in this Addendum.

LEGAL NOTICES

In India there are laws dealing with certain of the substances which are the subject of monographs which follow. These monographs should be read subject to the restrictions imposed by those laws wherever they are applicable.

It is expedient that enquiry be made in each case in order to ensure that the provisions of any law are being complied with.

In general, the Drugs & Cosmetics Act, 1940, the Dangerous Drugs Act, 1930, and the Poisons Act, 1919, and the rules framed thereunder should be consulted.

Under the Drugs & Cosmetics Act, the Indian Pharmacopoeia is the book of standards for drugs included therein and the standards as included in the Indian Pharmacopoeia would be official. If considered necessary these standards can be amended and the Secretary of the Indian Pharmacopoeia Committee is authorised to issue such amendments. Whenever such amendments are issued, the Indian Pharmacopoeia would be deemed to have been amended accordingly.

PATENTS AND TRADEMARKS

The inclusion in the Indian Pharmacopoeia of any drug subject to actual, or potential, patent or similar rights, or the inclusion of any name which is a trademark in any part of the world does not and shall not be deemed to imply or convey permission, authority, or licence to exercise any right or privilege protected by such patent or trademark, including licence to manufacture, without due permission, authority, or licence from the person or persons in whom such rights and privileges are vested.

Preface

This Addendum amends the Indian Pharmacopoeia 1985 and is published by Government of India, Ministry of Health & Family Welfare on the recommendation of Indian Pharmacopoeia Committee (in accordance with Drugs & Cosmetics Act, 1940, Dangerous Drugs Act, 1930 and the Poisons Act, 1919, and the rules framed thereunder).

The Government of India constituted a permanent Indian Pharmacopoeia Committee in 1948 for the preparation of the Indian Pharmacopoeia and keeping it up-to-date. The first edition of the Indian Pharmacopoeia was published in 1955, followed by a Supplement in 1960. The second edition of the Indian Pharmacopoeia and its supplement were published in 1966 and 1975 respectively. The third edition of the Indian Pharmacopoeia was published in 1985.

The Government of India, Ministry of Health & Family Welfare, vide Resolution No. X.19014/2/83-DMS & PFA dated 18th January, 1984 reconstituted the Indian Pharmacopoeia Committee with the following as members for a term of five years for the purpose of compilation of the Supplement to the third edition of the Indian Pharmacopoeia:

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F.N.C.C.P.
Professor & Head, Deptt. of Medicine
All India Institute of Medical Sciences
Ansari Nagar
New Delhi 110 029

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Acknowledgement

The Govt. of India, Ministry of Health and Family Welfare, wish to express their appreciation of the work done by the Chairman and members of the Indian Pharmacopoeia Committee, members of its sub-committees and cooperation afforded by many fellow workers and the institutions.

The profound gratitude is expressed by the Indian Pharmacopoeia Committee to the Editor-in-Chief, Publications & Information Directorate, Council of Scientific & Industrial Research, New Delhi for accepting this job.

Shri S.N. Saxena, Production Officer, and Smt. Supriya Gupta of Publications & Information Directorate deserve special appreciation for their keen interest in the execution of this job and maintaining standard of fine production.

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Contents

VOLUME ONE

Page
Legal Notices .... (v)
Preface .... (vii)
Acknowledgements .... (xi)
Introduction .... (xv)
General Notices 1
Monographs (A—P) 15

VOLUME TWO

Monographs (Q—Z) 433
APPENDICES A-1
Contents of Appendices A-3
INDEX I-1

ADDENDUM (I)

Notices v
Preface vii
Introduction xii
Amendments to the Monographs 1
Monographs 25
APPENDICES A-1
Contents of Appendices A-3
INDEX I-1

Introduction

The third edition of Pharmacopoeia of India was published in 1985. As a number of new drugs have been introduced in medical practice an Addendum is being issued to provide official standards for such new drugs and amendments to the Indian Pharmacopoeia 1985 are also being included in this Addendum.

The Addendum adds to the Pharmacopoeia 46 new monographs and makes amendments to the monographs and appendices currently official.

New drugs included in this Addendum are the adrenocortical steroids Beclomethasone Dipropionate and Hydrocortisone Hydrogen Succinate, the analgesic Pentazocine, the antidepressant Doxepine Hydrochloride, the antifungal Miconazole Nitrate and Clotrimazole, the antiemetic Metoclopramide Hydrochloride, the anti-inflammatory and analgesic Naproxen, the antipsychotic Haloperidol, the bronchodilator Salbutamol, the general anaesthetic Halothane, the hypnotic and sedative Nitrazepam, the vasodilator and antianginal Diluted Pentaerythritol Tetranitrate and the pharmaceutical aid Glycine and Dextrin.

Preparation of some substances referred to above are added, for example, Doxepin Capsules, Haloperidol Tablets, Metoclopramide Tablets, Naproxen Tablets, Pentaerythritol Tablets, Pentazocine Injection, Salbutamol Inhaler and Salbutamol Injection.

Several new preparation of substances already included in the Pharmacopoeia have been included, for example, Carbimazole Tablets, Clonidine Injection, Colchicine Tablets, Ethosuximide Capsules, Isoxsuprine Injection, Isoxsuprine Tablets, Lignocaine Hydrochloride Injection, Mercaptopurine Tablets, Metformin Tablets, Propantheline Tablets, Dextropropoxyphene Capsules, Propranolol Injection, Spironolactone Tablets, Trifluoperazine Tablets, Triflupromazine Tablets and Amoxicillin for Oral Suspension.

The monographs on Typhoid Paratyphoid A Vaccine, Typhoid Vaccine (for children), and Aerosols have also been included in the Addendum.

A challenge test to evaluate the efficacy of antimicrobial preservatives in pharmaceutical products has been included in the Addendum as Appendix 4.8. It is stressed that the test is not a mandatory requirement to be applied to preparations of Pharmacopoeia, it is offered as a means by which the suitability of an intended preservative system for a product may be assessed during the development of that product.

A specific Agglutination Test for identity of Typhoid and Typhoid Paratyphoid A Vaccines has also been included in the Addendum as Appendix 2.42.

Additions

The following monographs are added to the Indian Pharmacopoeia, 1985 by means of this Addendum:

Aerosols
Amoxycillin for Oral Suspension
Beclomethasone Dipropionate
Carbimazole Tablets
Clonidine Injection
Clotrimazole
Colchicine Tablets
Dextrin
Dextropropoxyphene Capsules
Doxepin Hydrochloride
Doxepin Capsules
Ethosuximide Capsules
Glycine
Haloperidol
Haloperidol Tablets
Halothane
Hydrocortisone Hydrogen Succinate
Isoxsuprine Injection
Isoxsuprine Tablets
Lignocaine Hydrochloride Injection
Mercaptopurine Tablets
Metformin Tablets
Metoclopramide Hydrochloride
Metoclopramide Injection
Metoclopramide Tablets
Miconazole Nitrate
Naproxen
Naproxen Tablets
Nitrazepam
Nitrazepam Tablets
Diluted Pentaerythritol Tetranitrate
Pentaerythritol Tablets
Pentazocine
Pentazocine Injection
Pentazocine Tablets

Promethazine Injection
Propantheline Tablets
Propranolol Injection
Salbutamol
Salbutamol Inhaler
Salbutamol Injection
Spironolactone Tablets
Trifluoperazine Tablets
Trifluopromazine Tablets
Typhoid Paratyphoid A Vaccine
Typhoid Vaccine (For children)

Amendments

The following monographs of the Indian Pharmacopoeia 1985 are amended by the Addendum:

Aluminium Hydroxide Gel
Dried Aluminium Hydroxide Gel
Aminocaproic Acid
Ampicillin Injection
Analgin
Soluble Aspirin Tablets
Benzyl benzoate
Benzyl Benzoate Application
Bisacodyl Tablets
Whole Human Blood
Boric Acid
Calcium Carbonate
Calcium Lactate
Dibasic Calcium Phosphate
Carbenicillin Injection
Carbimazole Tablets
Microcrystalline Cellulose
Cephalexin
Chlordiazepoxide
Chlorocresol
Chloroform
Chloroform Spirit
Chloroquine Phosphate
Chloroquine Phosphate Tablets
Cholecalciferol
Cholera Vaccine
Anhydrous Citric Acid
Clonidine Hydrochloride
Clonidine Injection
Clonidine Tablets
Cloxacillin Sodium
Cloxacillin Injection
Cyclophosphamide Tablets

Amendments *(Contd.)*

Cyproheptadine Tablets
Dapsone
Demethylchlortetracycline Hydrochloride
Diloxanide Furoate Tablets
Diphenhydramine Hydrochloride
Diphtheria and Tetanus Vaccine (Adsorbed)
Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed)
Ephedrine Hydrochloride
Ephedrine Tablets
Erythromycin Tablets
Erythromycin Estolate
Erythromycin Estolate Tablets
Erythromycin Stearate
Ethambutol Hydrochloride
Anaesthetic Ether
Ethinylestradiol
Eucalyptus Oil
Ferrous Gluconate
Frusemide Injection
Gelatin
Gentamicin Sulphate
Gentamicin Injection
Glycerin
Griseofulvin
Hydrochlorothiazide
Hydrocortisone Acetate
Injections
Intraperitoneal Dialysis Fluid
Isoniazid
Diluted Isosorbide Dinitrate
Lactose
Lignocaine and Adrenaline Injection
Absorbent Lint
Mannitol
Measles Vaccine Live
Methyl Salicylate
Methyldopa
Metronidazole Benzoate
Nikethamide
Nystatin
Nystatin Ointment
Nystatin Tablets
Nystatin Vaginal Tablets
Oxygen
Oxyphenbutazone
Oxytetracycline
Oxytetracycline Hydrochloride Injection
Hard Paraffin

Amendments *(contd.)*

Pepsin
Phenylbutazone
Phenylbutazone Tablets
Phthalylsulphathiazole
Poliomyelitis Vaccine (Oral)
Potassium Iodide
Prednisolone Acetate
Prednisolone Tablets
Procaine Penicillin
Dextropropoxyphene Hydrochloride
Propranolol Hydrochloride
Quiniodochlor
Quiniodochlor Tablets
Rabies Vaccine
Riboflavine Phosphate Sodium
Rifampicin
Salbutamol Sulphate
Snake Venom Antiserum
Sodium Bicarbonate
Sodium Carboxymethyl Cellulose
Sodium Chloride
Sodium Citrate
Sodium Hydroxide
Sorbitol
Sorbitol Solution
Starch
Streptomycin Sulphate
Succinylcholine Chloride Injection
Sucrose
Sulphadimethoxine
Sulphadimidine Sodium
Sulphadoxine
Sulphamethoxazole
Sulphaphenazole
Tetanus Vaccine (Adsorbed)
Tetracycline
Tetracycline Eye Ointment
Tetracycline Injection
Thiamine Hydrochloride
Powdered Tragacanth
Triamcinolone
Trimethoprim
Typhoid Vaccine
Purified Water
Yellow Fever Vaccine

Amendments to the Monographs

Introduction Page (xvi)	**Line 13** For ‘Ethinyloestradiol Tablets’ read ‘Ethinylestradiol Tablets’
	Line 32 After ‘Lithium Carbonate’ insert ‘Phenylbutazone’
Page (xviii)	**Lines 35 and 36** For ‘Anticoagulant Sodium Citrate Injection’ read ‘Anticoagulant Sodium Citrate Solution’
Page (xxi)	After ‘Iodoxyl Injection’ add ‘Ipecacuanha’
Aluminium Hydroxide Gel Page 25	**Ammonium salts** Delete the test
Dried Aluminium Hydroxide Gel Page 26	**Ammonium salts** Delete the test
Aminocaproic Acid Page 29	**Assay—Line 7** For ‘0.015120’ read ‘0.01312’
Ampicillin Injection Page 41	**Dose—Line 1** After ‘intramuscular’ insert ‘or intravenous’
Analgin Page 44	**Aminoantipyrine—Line 7** After ‘gradually’ insert ‘but not an orange or pink colour’
Soluble Aspirin Tablets Page 51	**Standards—Line 5** For ‘Citric Acid’ read ‘Anhydrous Citric Acid’
Benzyl Benzoate Page 67	**Refractive index—Line 1** For ‘1.5668 and 1.5670’ read ‘1.567 and 1.569’
Benzyl Benzoate Application Page 67	After **‘Storage’** add the following: **Labelling:** The label on the container states that the contents should be shaken before use.

Bisacodyl Tablets
Page 76

Other requirements—Line 2
For 'tablets'
read 'Tablets'

After **Other requirements** add the following:
Disintegration: Comply with the **disintegration test for tablets, Method** (3), Appendix 5.6.1, using a 1.5 per cent w/v solution of *sodium bicarbonate* in place of mixed phosphate buffer pH 6.8.

Whole Human Blood
Page 77

Storage—Line 3
For 'Store at a temperature between 1° and 6° and held constant within 2° range and during transit, between 1° and 10°,
read 'Store continuously at a temperature between 4° and 6°'

Boric Acid
Page 78

Clarity and colour of solution
Change the statement to :
Clarity of solution: The solution obtained in **Identification** test (B) is almost clear or not more than slightly opalescent.

Sulphate—Lines 1 and 2
For '30 ml of *water* and 1 ml of *hydrochloric acid*'
read '60 ml of *water* and 2 ml of *hydrochloric acid*'

Loss on drying—Line 2
For '100 g'
read '1.0 g'

Calcium Carbonate
Page 84

Magnesium and alkali metals—Lines 4 and 5
Delete the words 'add 2 ml of *acetic acid*'

Barium—Line 1
For '*dilute acetic acid*'
read '*2N acetic acid*'

Calcium Lactate
Page 87

Standards—Line 5
For 'anhydrous'
read 'dried'

Water—Line 1
For Water
read 'Loss on drying'

Lines 2 and 3
For 'Appendix 3.3.25'
read 'Appendix 5.8'

Dibasic Calcium Phosphate
Page 89

Standards—Line 3
For '30.9 per cent'
read '30.0 per cent'

Page 90

Assay—Line 7
For '23 ml'
read '20 ml'

Line 8
For '*sodium hydroxide solution*'
read '*10N sodium hydroxide*'

Carbenicillin Injection
Page 94

Storage—Lines 2 and 3
For 'immediately after preparation'
read 'within twenty-four hours of preparation'

Microcrystalline Cellulose
Page 96

Assay—Line 10
For '*orthophenanthroline solution*'
read '*ferroin sulphate solution*'

Line 15
For '0.00338 g of cellulose'
read '0.000676 g of cellulose in the portion titrated'

Cephalexin
Page 98

pH—Line 1
For '5.0 per cent'
read '0.5 per cent'

Undue toxicity
Change the statement to:
Complies with the test described under Bacitracin, using 0.5 ml of a suspension containing 5 mg of Cephalexin in a 0.5 per cent w/v solution of *methylcellulose (4000 cps)*, administered orally by means of a canula or other suitable device and observing the mice for 7 days.

Chlordiazepoxide
Page 109

Melting range
Delete the test

Chlorocresol
Page 110

Solubility—Lines 1 and 2
Delete the words 'soluble in hot *water*'

Chloroform
Page 111

Wt. per ml—Line 1
For '1.474 and 1.478g'
read '1.465 and 1.470 g'

Chloroform Spirit
Page 111

Description—Line 2
For 'teste sweet'
read 'taste sweet'

Chloroquine Phosphate
Page 113

Identification (D)—Line 4
For ‘about 0.6’
read ‘about 0.44’

Related substances—Line 8
For ‘0.050 per cent’
read ‘0.075 per cent’

Chloroquine Phosphate Tablets
Page 114

Dose—Line 4
For ‘500 ng’
read ‘500 mg’

Line 5
For ‘75 mg’
read ‘750 mg’

Cholecalciferol
Page 123

Identification (C)—Lines 7 and 8
For ‘50 mg’
read ‘50 mg per ml’

Cholera Vaccine
Page 123

Dose—Line 2
For ‘1 ml’
read ‘0.5 ml’

Standards—Lines 16 to 20
For ‘The vaccine may contain a preservative. It contains not less than 12,000 million bacteria per human dose which does not exceed 1 ml.’ read ‘The vaccine may contain a suitable preservative. It contains not less than 12,000 million bacteria per ml.’

Anhydrous Citric Acid
Page 127

Readily carbonisable substances
Change the statement to:
Heat 0.75 g with 10 ml of *sulphuric acid* (containing between 94.5 and 95.5 per cent w/w of H_2SO_4) in a water-bath maintained at 90° ± 1°. Shake after one minute, continue the heating for a total of one hour and cool rapidly and immediately. Any colour produced is not deeper than that of a mixture of 1.0 ml of *cobalt chloride C.S.* and 9.0 ml of *ferric chloride C.S.*

Clonidine Hydrochloride
Page 130

Identification (D)—Line 1
After ‘305’’
add the following: ‘with decomposition’

Line 2
After ‘313’’
add the following : ‘with decomposition

Clonidine Tablets
Page 130

Uniformity of content—Line 3
For '*dilute acetic acid*'
read 'a 10 per cent v/v solution of *acetic acid*'

Line 4
For '0.1 per cent'
read '0.2 per cent'

Assay—Line 4
For '*dilute acetic acid*'
read 'a 10 per cent v/v solution of *acetic acid*'

Line 5
For '0.1 per cent'
read '0.2 per cent'

Cloxacillin Sodium
Page 131

Identification (C)
Delete the test

Light absorption
Delete the test

Chlorine—Line 1
For '7.5 per cent'
read '8.0 per cent'

After the test for **Chlorine** add the following test:
Iodine-absorbing substances : Not more than 5 per cent, calculated with reference to the anhydrous substance and determined by the following method. Dissolve 0.125 g in sufficient *mixed phosphate buffer pH 4.0* to produce 25.0 ml. To 10.0 ml add 10 ml of *mixed phosphate buffer pH 4.0* and 10.0 ml of *0.01N iodine* and titrate immediately with *0.01N sodium thiosulphate* using *starch solution* added towards the end of the titration, as indicator. Repeat the operation without the substance being examined, the difference between the titrations represents the amount of iodine-absorbing substances present. Each ml of *0.01N Sodium thiosulphate* is equivalent to 0.504 mg of iodine-absorbing substances.

Cloxacillin Injection
Page 132

Storage—Lines 2 and 3
For 'thirty minutes'
read 'twenty-four hours'

Cyclophosphamide Tablets
Page 145

Assay—Lines 4 and 6
For '*solvent ether*'
read '*chloroform*'

Line 7
For 'ethereal solutions to a long-necked flask, remove the *ether*'
read 'extracts to a long-necked flask, remove the *chloroform*'

Cyproheptadine Tablets
Page 148

Assay
Change the statement to:
Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 3 mg of anhydrous cyproheptadine hydrochloride, add 100 ml of *0.1N sulphuric acid,* and shake for fifteen minutes. Add sufficient *0.1N sulphuric acid* to produce 200.0 ml, mix well and filter. Measure the *extinction* of a 1-cm layer of the filtrate at the maximum at about 285 nm, Appendix 5.15A, using *0.1N sulphuric acid* as the blank.

Calculate the content of $C_{21}H_{21}N,HCl$, taking 355 as the value of E(1 per cent, 1 cm) at the maximum at about 285 nm.

Dapsone
Page 149

Identification (A)—Line 2
For '0.005 per cent w/v'
read '0.0005 per cent w/v'

Demethylchlortetracycline Hydrochloride
Page 152

Light absorption—Line 1
For '0.01 per cent'
read '0.1 per cent'

Diloxanide Furoate Tablets
Page 174

Identification
Change the statement to:
Triturate a quantity of the powdered tablets equivalent to 250 mg of Diloxanide Furoate with 20 ml of *chloroform* and filter. Evaporate the filtrate to dryness; the residue melts at about 115°, Appendix 5.11, and complies with **Identification** test (A) described under Diloxanide Furoate.

Assay—Line 3
For '25.0 ml'
read '250.0 ml'

Diphenhydramine Hydrochloride
Page 178

Related substances—Lines 10 and 11
For 'a 20 per cent v/v solution of *sulphuric acid* in *alcohol*'
read '*sulphuric acid*'

Diphtheria and Tetanus Vaccine (Adsorbed)
Page 181

Identification
Add the following:
The identity of diphtheria and tetanus toxoids can also be demonstrated by in vitro methods such as flocculation or double immuno-diffusion tests.

pH—Line 1
For '6.5'
read '6.0'

Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed)

Page 182

Identification (B)
Add the following:
The identity of the pertussis component can also be demonstrated by suitable in vitro methods such as the agglutination test, Appendix 2.42.

pH—Line 1
For '6.7 and 7.3'
read '6.0 and 7.0'

Thiomersal—Line 1
For '0.005 per cent'
read '0.02 per cent'

Specific toxicity—Lines 1 and 2
For 'Tetanus Vaccine (Adsorbed)'
read 'Diphtheria and Tetanus Vaccine (Adsorbed)'

Ephedrine Hydrochloride

Page 187

Identification (A)
Change the statement to :
The light absorption, in the range 220 to 350 nm of a 1-cm layer of a 0.05 per cent w/v solution exhibits maxima at about 251 nm, 257 nm and 263 nm; *extinction* at 251 nm, about 0.30; at 257 nm, about 0.49; at 263 nm, about 0.37, Appendix 5.15A.

Ephedrine Tablets

Page 188

Assay
Change the statement to:
Weigh not less than 50 tablets and reduce to a fine powder. Weigh accurately a quantity of the powder equivalent to about 1.2 g of Ephedrine Hydrochloride and transfer to a glass stoppered conical flask, add 50.0 ml of *0.1 N Sulphuric acid,* shake the mixture and filter, rejecting the first 20 ml of the filtrate. Transfer 10.0 ml of the filtrate to a separator. Saturate the solution with *sodium chloride* (about 3.0 g) add 5 ml of *dilute sodium hydroxide* solution and extract with four 25 ml portions of chloroform. Wash the combined *chloroform* extracts by shaking with 10 ml of saturated solution of *sodium chloride* and filter through chloroform-washed cotton into a beaker. Extract the washed solution with 10 ml of *chloroform,* and add to the main chloroform extract. Titrate with *0.1N perchloric acid* using *solution of methyl red* as indicator. Perform a blank determination and make any necessary correction. Each ml of *0.1 N perchloric acid* is equivalent to 0.02017 g of $C_{10}H_{15}NO,HCl$.

Erythromycin
Page 193

Assay—Line 2
For *'water'*
read *'buffer solution No.2,* Appendix 4.1, TABLE 2.

Erythromycin Tablets
Page 194

Assay—Line 3
For *'water'*
read *'buffer solution No.2,* Appendix 4.1, TABLE 2.

Erythromycin Estolate
Page 194

Undue toxicity—Line 4
After 'erythromycin'
add 'administering orally by means of a canula or other suitable device.'

Assay—Line 2
For 'and add 20 ml of *buffer solution pH 7.0* and sufficient *water* to produce 100.0 ml'
read 'and add sufficient *buffer solution No.2,* Appendix 4.1, TABLE 2, to produce 100.0 ml.'

Erythromycin Estolate Tablets
Page 195

Assay—Line 3
For 'and 200 ml of *buffer solution pH 7.0'*
read 'and 200 ml of *buffer solution No. 2,* Appendix 4.1, TABLE 2'.

Erythromycin Stearate
Page 196

Undue toxicity—Line 5
After 'sample'
add 'administering orally by means of a canula or other suitable device.'

Ethambutol Hydrochloride
Page 198

Specific optical rotation—Line 1
For 'Between + 6.0° and + 6.6°'
read 'Between + 5.8° and + 6.6°'

Anaesthetic Ether
Page 199

Boiling range
For '34°'
read '35°'

Specific gravity—Line 1
For '0.713'
read '0.714'

Acetone and aldehyde—Line 6
After 'five minutes'
add 'in the dark'

Ethinylestradiol
Page 200

Before **Dose** insert the following:
Category: Estrogen

Eucalyptus Oil
Page 208

Standards—Line 5
For '65.0 per cent w/w'
read '60.0 per cent w/w'

Ferrous Gluconate
Page 214

Loss on drying—Line 3
For 'four hours'
read 'sixteen hours'

Assay—Line 9
For '*ferrous sulphate solution*'
read '*ferroin sulphate solution*

Frusemide Injection
Page 224

Free amine—Line 5
Add the following:
The *extinction* is not more than 0.3.

Gelatin
Page 229

Microbial limits—Line 3
For '*E. coil*'
read '*E.coli*'

Gentamicin Sulphate
Page 230

Solubility
Change the statement to:
Soluble in *water*; practically insoluble in *alcohol, chloroform* and in *solvent ether*.

Assay—Line 5
After 'administration'
insert 'or for the preparation of Eye Drops, without further sterilisation'

Undue toxicity—Line 4
For '*water for injection*'
read '*saline solution*'

Gentamicin Injection
Page 231

Undue toxicity—Line 4
For '*water for injection*'
read '*saline solution*'

Glycerin
Page 234

Sugar
Change the statement to:
Heat 10 ml of a 50 per cent w/v solution with 1 ml of *2N sulphuric acid* on a water-bath for five minutes. Add 2 ml of *2N sodium hydroxide* and 1 ml of *copper sulphate solution*. A blue coloured solution is produced. Continue heating on a water-bath for five minutes. The solution remains bluish-green and no red precipitate is formed.

Griseofulvin
Page 236

Specific surface area
Delete the test.

Hydrochlorothiazide
Page 244

Identification (B)—Line 1
For '13 mg'
read '10 mg'

Hydrocortisone Acetate
Page 246

Loss on drying—Line 1
For '0.1 per cent'
read '1.0 per cent'

Injections
Page 256

Appearance—Para 2 Line 4
For 'of a uniform suspension'
read 'or a uniform suspension'

Page 257

Uniformity of weight—Line 1
For '7'
read '6'

Content of active ingredient—Line 1
For '8'
read '7'

TABLE OF DEVIATIONS—Line 2
for 'lable'
read 'label'

Intraperitoneal Dialysis Fluid
Page 264

Assay: (5) *For dextrose*
Change the statement to:
Transfer 5.0 ml in a stoppered flask and carry out the assay for the content of dextrose under Dextran-40 injection. Commencing with the words, "add 25 ml of a buffer solution..."

Isoniazid
Page 268

Loss on drying—Line 1
For 'Not more than 1.0 per cent, Appendix 5.8'
read 'Not more than 1.0 per cent, determined on 1.0 g by drying in an oven at 105°, Appendix 5.8'

Diluted Isosorbide Dinitrate

Page 271

Description—Line 1
For 'Ivory-white, crystalline, powder'
read 'Ivory-white powder'

Solubility
Delete the test.

Lactose
Page 278

Clarity, colour and odour of the solution—Line 2
After 'colourless'
add 'or nearly colourless'.

Specific optical rotation—Lines 1 and 2
After 'Between + 54.8° and + 55.5°'
insert 'calculated on the anhydrous basis'

Lignocaine and Adrenaline Injection
Page 284

After the test for **pH** add the following:
Other requirements : Complies with the requirements stated under injections.

Absorbent Lint
Page 286

Description—Line 4
For 'nap'
read 'nep'

Line 5
For 'naps'
read 'neps'

Standards—Line 2
For 'nap'
read 'nep'

Mannitol
Page 294

Specific optical rotation
Change the statement to:
Between + 137° and + 145°, determined in a solution prepared by adding to about 1 g, accurately weighed, 40 ml of a 10 per cent w/v solution of *ammonium molybdate* (previously filtered, if necessary), 20 ml of *N sulphuric acid* and sufficient *water* to produce 100.0 ml, Appendix 5.12.

Measles Vaccine Live
Page 295

Standards—Para 3, Line 10
For 'pH indicator'
read 'pH indicator such as phenol red and also permitted antibiotics in the smallest effective concentration.'

Identification
Delete the second and third paragraphs.

Page 296

Potency—Line 1
For 'inject'
read 'infect'

After the test for **Potency** insert the following:
Stability : Incubate the freeze-dried vaccine at 37° for seven days. At the end of this period reconstitute the vaccine and compare the virus titre with that of the vaccine stored at –20° or below and reconstituted in the same manner.

The vaccine passes the test if

(1) after incubation it retains at least 1000 $TCID_{50}$ per human dose, and

(2) during incubation the virus titre does not decrease by more than

1.0 Log_{10} $TCID_{50}$ per human dose.

Methyl Salicylate

Page 313

Wt. per ml

Change the statement to:

Between 1.175 and 1.185 g, Appendix 5.19.

Methyldopa

Page 315

Related substances

Change the statement to :

Carry out the method for *thin-layer chromatography,* Appendix 5.4.3, using *microcrystalline cellulose* as the coating substance and a mixture of 65 volumes of *n-butyl alcohol,* 25 volumes of *water* and 15 volumes of *glacial acetic acid* as the mobile phase, allowing the solvent front to ascend 10 cm above the line of application. Apply separately to the plate the following three solutions, (1) 10 µl of a 1.0 per cent w/v solution of the substance being examined, in a mixture of 4 volumes of *7N hydrochloric acid* and 96 volumes of *methyl alcohol,* (2) 10 µl of a 0.005 per cent w/v solution of *3-methoxymethyldopa* R.S. in *methyl alcohol,* (3) 20 µl of a mixture of equal volumes of solutions (1) and (2). After removal of the plate, dry it immediately in a current of warm air and spray with a mixture of 5 volumes of a 5 per cent w/v solution of *sodium nitrite* and 45 volumes of a 0.3 per cent w/v solution of *4-nitro aniline* in a mixture of 80 volumes of *hydrochloric acid* and 20 volumes of *water.* Dry it immediately in a current of warm air and spray with a 20 per cent w/v solution of *sodium carbonate.* Any spot in the chromatogram obtained with solution (1) other than the principal spot is not more intense than the spot in the chromatogram obtained with solution (2). The test is valid only if the chromatogram obtained with solution (3) shows two clearly separated spots.

Metronidazole Benzoate

Page 320

Identification (B)

For 'reactions of *benzoates*'

Read 'reaction (B) of *benzoates*'

Solubility—Line 1

For 'Sparingly soluble'

read 'Very slightly soluble'

Free benzoic acid—Line 3

For '0.1N *sodium hydroxide*'

read '0.01N *sodium hydroxide*'

Line 6

For '0.01221 g'

read '0.001221 g'

Nikethamide

Page 335

Refractive index

For 'Between 1.524 and 1.526'

read 'Between 1.522 and 1.524'

Nystatin
Page 343

Assay—Para 2, Line 3
For 'with a solution containing 9.56 per cent w/v of *potassium dihydrogen phosphate* and 11.5 per cent v/v of *N potassium hydroxide'*
read 'with *buffer solution No. 4,* Appendix 4.1, TABLE 2.

Nystatin Ointment
Page 343

Assay—Line 7
For 'with *buffer solution pH 6.0'*
read 'with *buffer solution No. 4,* Appendix 4.1, TABLE 2.'

Nystatin Tablets
Page 344

Assay—Line 5
For 'with a solution containing 9.56 per cent w/v of *potassium dihydrogen phosphate* and 11.5 per cent v/v of *N potassium hydroxide'*
read 'with *buffer solution No. 4,* Appendix 4.1, TABLE 2.'

Nystatin Vaginal Tablets
Page 344

Assay—Line 5
For 'with *buffer solution pH 6.0'*
read 'with *buffer solution No. 4,* Appendix 4.1, TABLE 2.'

Oxygen
Page 350

Solubility—Line 1
For '700 Torr'
read '760 Torr'

Carbon dioxide—Line 1
For '30 parts per million'
read '300 parts per million'

Assay
Change the statement to:
Carry out the *assay of oxygen,* Appendix 3.3.8., using 100 ml of oxygen and placing spirals of freshly cleaned copper wire and 125 ml of ammonia buffer pH 10.9. The volume of the residual gas in the burette is not greater than 1.0 ml.

Oxyphenbutazone
Page 351

Identification (B)—Line 2
For '0.01M'
read '0.01N'

Oxytetracycline
Page 353

pH—Line 1
For '5.0'
read '4.5'

Oxytetracycline Hydrochloride Injection
Page 356

Usual strength—Line 2
For 'tetracycline'
read 'oxytetracycline'

Content of tetracycline—Line 1
For '**Content of tetracycline**'
read '**Content of oxytetracycline**'

Line 7
For 'amount of tetracycline'
read 'amount of oxytetracycline'

pH—Line 1
For 'a 10 per cent w/v'
read 'a 10 per cent w/v solution'

Hard Paraffin
Page 360

Readily carbonisable substances
Delete the test.

Pepsin
Page 372

Acidity
Delete the test.

Residue on ignition—Line 1
For '0.5 per cent'
read '5.0 per cent'

Loss on drying
Change the statement to:
Not more than 5.0 per cent, determined on 1.0 g by drying in an oven at 105°, Appendix 5.8.

Phenylbutazone
Page 385

Chloride
Change the statement to:
Boil 2.0 g with 60 ml of *water* for five minutes, cool and filter. To 30 ml of the filtrate add 1 ml of *2N nitric acid* and 1 ml of *silver nitrate solution;* any opalescence produced is not greater than that from 0.1 ml of *0.02N hydrochloric acid* treated in the same manner.

Phenylbutazone Tablets
Page 385

Identification
Change the statement to:
Extract a quantity of the powdered tablets equivalent to 0.2 g of Phenylbutazone, with 40 ml of warm *acetone,* filter and evaporate the filtrate to dryness. The residue complies with **Identification** tests (A) and (B) described under Phenylbutazone.

Phthalylsulphathiazole
Page 390

Line 4
For '**Solubility**'
read '**Standards**'

After '**Description**' add the following:
Solubility : Practically insoluble in *water,* in *chloroform* and in *solvent ether;* slightly soluble in *alcohol.* Freely soluble in aqueous solutions of *alkali hydroxides* and *carbonates* and in *hydrochloric acid.*

Poliomyelitis Vaccine (Oral) Page 400	Change the monograph to revised monograph [P. 53]
Potassium Iodide Page 406	**Assay**—Line 9 For ‘0.0166 mg’ read ‘0.0166 g’
Prednisolone Acetate Page 408	**Light absorption**—Line 2 For ‘0.0001 per cent’ read ‘0.001 per cent’ Line 5 For ‘between 1.85 and 2.05’ read ‘between 1.50 and 1.75’
Prednisolone Tablets Page 408	**Usual strengths**—Before ‘5 mg’ insert ‘1 mg; 2 mg;’
Procaine Penicillin Page 415	**pH**—Line 1 For ‘30 per cent’ read ‘0.33 per cent’
Dextropropoxyphene Hydrochloride Page 424	**Specific optical rotation**—Line 1 For ‘Between + 52° and +57°’ read ‘Between +36° and +40°’
Propranolol Hydrochloride Page 425	**Identification(B)**—Line 4 For ‘360 nm’ read ‘306 nm’
Quiniodochlor Page 441	**Free iodine and iodide**—Lines 1 and 2 Delete the words ‘ a solution of 1 mg of *potassium iodide* in’
Quiniodochlor Tablets Page 442	**Assay**—Line 16 For ‘0.91 g’ read ‘0.975 g’

Rabies Vaccine
Page 443

Absence of Line virus
For 'line'
read 'live'

Riboflavine
Page 445

Specific optical rotation
Change the statement to:
Between –115° and –135°, determined at 20° on a 0.5 per cent w/v solution in *0.05N sodium hydroxide,* within thirty minutes after preparing the solution, Appendix 5.12.

Riboflavine Phosphate Sodium
Page 447

Standards—Line 4
For '77.0 per cent'
read '79.0 per cent'

Free phosphate—Line 10
After 'measure'
insert the words 'within fifteen minutes'

Lines 16 and 17
For '9.5 ml of *water* and 0.5 ml of a standard phosphate solution'
read '9.0 ml of *water* and 1.0 ml of a standard phosphate solution'

Rifampicin
Page 448

Related substances—Line 15
For 'spot'
read 'spots'

Line 16
For 'is'
read 'are'

Undue toxicity
Change the statement to:
Complies with the test described under Bacitracin, using 1.0 ml of a suspension containing 6 mg of Rifampicin in a 1.0 per cent w/v solution of *methylcellulose (4000 cps)* administered orally by means of a canula or other suitable device.

Salbutamol Sulphate
Page 450

Foreign substances—Line 1
For **'Foreign substances'**
read **'Related substances'**

Line 7
For *'methyl alcohol'*
read *'water'*

Snake Venom Antiserum

Page 460

Storage
Change the statement to :
For freeze-dried serum : Store in single-dose containers and avoid exposure to excessive heat.
For other preparations : Store in single-dose containers at a temperature between 2° and 8°.

Sodium Bicarbonate

Page 466

Aluminium, calcium and insoluble matter
Change the statement to:
Calcium : A 2.0 per cent w/v solution, when boiled for five minutes, is clear or at most slightly opalescent.

Heavy metals—Line 4
For '10 ml'
read '18 ml'

Sodium Carboxymethyl Cellulose

Page 467

Heavy metals—Line 1
For ' 10 ml'
read '40 ml'

Sodium Chloride

Page 467

Acidity or alkalinity—Line 4
For '*Phenol red solution*'
read '*bromothymol blue solution*'

Page 468

Sodium ferrocyanide
Change the statement to:
Ferrocyanide : Dissolve 2.0 g in 6 ml of *water* and 0.5 ml of a mixture of 5 ml of a 1 per cent w/v solution of *ferric ammonium sulphate* in a 0.25 per cent w/v solution of *sulphuric acid,* and 95 ml of a 1 per cent w/v solution of *ferrous sulphate.* No blue colour is produced within ten minutes.

Sodium Citrate

Page 472

Tartrate—Line 4
For 'no cyrstalline'
read 'no crystalline'

Sodium Hydroxide

Page 473

Assay—Line 10
For '0.106 g'
read '0.053 g'

Sorbitol

Page 478

Standards—Line 3
For '$C_6H_{14}O_6$'
read 'D-glucitol, $C_6H_{14}O_6$'

Sorbitol Solution

Page 479

Standards—Line 3
For 'total alcohols calculated as $C_6H_{14}O_6$'
read 'hexitols expressed as D-glucitol, $C_6H_{14}O_6$'

pH—Delete the test and insert the following:

Acidity or Alkalinity : To 7 g add sufficient freshly boiled and cooled *water* to produce 50 ml. To 10 ml of the resulting solution add 0.01 ml of *dilute phenolphthalein solution*; not more than 0.2 ml of *0.01N sodium hydroxide* is required to change the colour of the solution to pink. To a further 10 ml of the solution add 0.01 ml of *methyl red solution*; not more than 0.3 ml of *0.01N hydrochloric acid* is required to change the colour of the solution to red.

After **Heavy metals** add the following:
Nickel : Not more than 1 part per million, determined on 14 g as described under Sorbitol.

Total alcohols
For **'Total Alcohols'**
read **'Assay'**

Starch

Page 481

Microbial limits—Line 1
For 'meets the requirements'
read '1 g meets the requirements'

Streptomycin Sulphate

Page 484

Standards—Line 10
After $C_{21}H_{39}N_7O_{12}$, add the following:
'calculated with reference to the dried substance'

Undue toxicity—Line 3
For '1.0 mg'
read '0.75 mg'

Succinylcholine Chloride Injection

Page 487

After the test for **Hydrolysis products** add the following:
Other requirements : Complies with the requirements stated under Injections.

Sucrose

Page 489

Acidity or Alkalinity—Line 4
For '0.25'
read '0.35'

Calcium—Line 1
For '10.0 per cent'
read '5.0 per cent'

Reducing sugars
Change the statements to:
To 1 ml of a 50 per cent w/v solution add 4 ml of *water* and 5 ml of *potassium cupri-tartrate solution* and boil for fifteen seconds; no red precipitate is formed.

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Sulphadimethoxine
Page 492

Heavy metals—Line 2
For 'Method A'
read 'Method C'

पुस्तकालय
गुरुकुल कांगड़ी विश्वविद्यालय

Sulphadimidine Sodium
Page 494

Heavy metals—Line 2
For 'Method A'
read 'Method C'

Sulphadoxine
Page 495

Identification (C)
Change the statement to:
The light absorption, in the range 230 to 350 nm, of a 1-cm layer of a 0.006 per cent w/v solution in *0.1N sodium hydroxide* exhibits a maximum only at 272 nm; *extinction* at 272 nm, about 0.45, Appendix 5.15A.

Sulphamethoxazole
Page 498

Heavy metals—Line 2
For 'Method A'
read 'Method C'

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Sulphaphenazole
Page 498

Heavy metals—Line 2
For 'Method A'
read 'Method C'

Tetanus Vaccine (Adsorbed)
Page 505

Identification
After the first para add the following:
The identity of tetanus toxoids can also be demonstrated by in vitro methods such as flocculation or double immuno-diffusion tests.

pH—Line 1
For '6.2 and 6.8'
read '6.0 and 7.0'

Tetracycline
Page 507

Standards—Line 4
For 'potency not less than 975 µg'
read 'potency equivalent to not less than 975 µg'

Assay—Line 2
For 'anhydrous tetracycline'
read 'tetracycline hydrochloride'

Line 5
For 'tetracycline'
read 'tetracycline hydrochloride'

Tetracycline Eye Ointment
Page 508

Assay—Line 5
For *'buffer solution pH 4.5'*
read *'buffer solution No. 3,* Appendix 4.1, TABLE 2.'

Tetracycline Injection
Page 509

Dose
Delete the statement 'By intramuscular injection, 250 mg to 800 mg daily.'

Thiamine Hydrochloride
Page 515

Identification—Line 2
For '233 nm'
read '238 nm'

Line 3
For '267 nm'
read '262 nm'

For '0.68'
read '0.63'

Line 4
For '0.52'
read '0.57'

Powdered Tragacanth
Page 525

Microbial limits—Line 1
For '1.0 g if free'
read '1.0 g is free'

Triamcinalone
Page 526

Loss on drying—Line 1
For '0.2 per cent'
read '2.0 per cent'

Trimethoprim
Page 530

Related substances—Line 2
For *'silica gel G'*
read *'silica gel GF 254'*

Typhoid Vaccine
Page 536

Dose—Line 2
For '1 ml'
read '0.5 ml'

Standards
In the first para the following may be added :
The vaccine may contain a suitable preservative.

Para 2, Lines 2 and 3
For 'per human dose which does not exceed 1 ml.'
read 'per ml'.

pH—Line 1
For '6.8'
read '6.0'

Potency
Delete the test.

Purified Water
Page 544

Chloride
Change the statement to:
To 15 ml add 1 ml of *dilute nitric acid* and 1 ml of *silver nitrate solution.* The opalescence produced is not more than that produced by treating a mixture of 1.5 ml of *standard* chloride solution and 13.5 ml of *water.*

Nitrates and nitrites
Change the statement to:
Nitrates : To 5 ml in a test-tube immersed in ice-water, add 0.4 ml of a 10 per cent w/v solution of *potassium chloride,* 0.1 ml of *diphenylamine solution* and, drop-wise with shaking, 0.5 ml of *sulphuric acid.* Transfer the tube to water-bath at 50° and allow to stand for fifteen minutes; any blue colour in the solution is not more intense than that in a solution prepared at the same time and in the same manner using a mixture of 4.5 ml of *nitrate-free water* and 0.5 ml of a solution prepared by diluting 1.0 ml of a 0.0326 per cent w/v solution of *potassium nitrate* with *water* to 1000.0 ml.

Yellow Fever Vaccine
Page 547

Standards—Line 3
For '170'
read '17 D'

Line 11
For 'and seed'
read 'and secondary seed'

Page 548

Undue toxicity
Change the statement to :
Inject intraperitoneally ten times the human dose into each of two guinea-pigs weighing between 250 g and 350 g, and one human dose but not more than 1 ml into each of five mice weighing between 17 g and 22 g; no symptoms of toxicity occur within seven days.

Monographs

Aerosols

Aerosols are dosage forms containing therapeutically active ingredients that are packaged under pressure in a sealed container and are released as a fine mist of spray upon activation of a suitable valve system. They are intended for local or systemic inhalation into the lungs or for topical application to the skin or various body orifices.

The basic components of an aerosol system are the container, the propellant, the concentrate containing the active ingredient(s), the valve and actuator.

Aerosols are of two types, the two-phase system consisting of gas and liquid or the three-phase system consisting of gas, liquid and solid or liquid. The two-phase aerosol comprises a solution of active ingredient(s) in liquified propellant and the vapourised propellant. The solvent is usually the propellant or a mixture of the propellant and co-solvents such as alcohol, propylene glycol and polyethylene glycols. The three-phase aerosol consists of a suspension or emulsion of the active ingredient(s) and the vapourised propellants. In the suspension the active ingredient(s) may be dispersed in the propellant system with the aid of suitable pharmaceutical aids such as wetting agents, solid carriers, etc. Foam aerosols contain an emulsion of the active ingredient(s), surface-active agents, aqueous or non-aqueous liquids and the propellants.

Active ingredients: For satisfactory bioavailability the active ingredient should have the majority of particles under 10 µm in size in the case of inhalation aerosols and upto 100 µm for other types of aerosols.

Propellants: Propellants perform the essential function of expelling the material from the container by supplying the necessary pressure within the aerosol system. They are liquified or compounded gases having vapour pressures exceeding atmospheric pressure. The commonly used propellants in aerosol systems are hydrocarbons, especially the fluorochloro-derivatives of methane and ethane, the butanes and pentanes and compressed gases such as nitrogen and carbon dioxide. Mixtures of propellants are often employed to obtain the necessary delivery and spray characteristics of the aerosol.

Valves: The valve regulates the flow of the active ingredient and propellant from the container and determines the spray characteristics of the aerosol. It must be manufactured from materials which are inert to the contents of the aerosol. The commonly used materials are rubber, plastic, aluminium and stainless steel.

For topical products, valves capable of providing continuous spray operation are suitable. However, products for oral or nasal inhalation require metered-dose valves which ensure delivery of a uniform quantity of spray and an accurate dose of the active ingredient(s), both within specified tolerances, with each activation of the valve. Metered valves may need priming before use if the aerosol packages have not been stored properly or have not been used for long periods of time.

Actuators: The actuator or adaptor which is fitted to the aerosol valve stem is a device which on depression or other movement opens the valve and directs the spray to the desired area. The design of the actuator which incorporates an orifice of varying size and shape and the expansion chamber is very important in influencing the physical characteristics of the spray or foam, particularly in the case of inhalation aerosols, where the active ingredient(s) must be delivered in the proper particle size range.

Containers: Aerosol containers are made of metal (stainless steel, aluminium or tin-plated steel), glass or plastic or a combination of these materials. The containers must be so designed that they provide the maximum in pressure safety and impact resistance.

PREPARATION OF AEROSOLS

Aerosols are commonly prepared by filling under pressure and sometimes by filling after refrigeration to temperatures below 0°. In filling under pressure, the requisite volume of the concentrate of the active ingredient(s) is filled in the container and either the propellant is forced under pressure through the valve orifice after the valve is sealed, or the propellant is allowed to flow under the valve cap and then valve assembly is sealed. In either case, the air in the container must be evacuated by means of vacuum or displacement with a small amount of the propellant.

Aerosol products should be manufactured under strictly controlled conditions and subjected to process controls which include propellant and medicament fill weights and pressure test and leak test of the finished product.

REQUIREMENTS OF TESTS

Leak Test : Select 12 aerosol containers at random, weigh each container to the nearest mg and record the weight, in mg, of each container as W_1. Allow the containers to stand in an upright position at room temperature for not less than 3 days and again weigh each container, recording the weight, in mg, of each as W_2. Determine the time T, in hours, during which the containers were under test. Calculate the leakage rate, in mg per year, of each container from the formula $(365)(24/T)(W_1 - W_2)$.

Determine the net fill weight of each of the containers tested by emptying the contents of each container, using a safe technique. Remove any residual contents by rinsing with a suitable solvent and finally rinsing with *methyl alcohol.* Retain all the components of each container and heat them at 80° for 5 minutes. Cool, weigh, and record the weight as W_3. The net fill weight is obtained from the formula $(W_1 - W_3)$.

The requirements of the test are met if the average leak rate of the 12 containers is not more than 3.5 per cent of the net fill weight per year and in none of the containers the leak rate is more than 5.0 per cent of the net fill weight per year. If one container leaks more than 5.0 per cent, and if none of the containers leaks more than 7.0 per cent per year, repeat the test on an additional 24 containers. In not more than 2 of the 36 containers, the leak rate is more than 5.0 per cent of the net fill weight per year and in none of the 36 containers, the leak rate is more than 7.0 per cent of the net fill weight per year.

GENERAL REQUIREMENTS

1. **Packaging :** The pressurised container is fitted with an actuator (adaptor) and the actuator body is fitted with a dust cap. The pack preferably carries an instruction leaflet.
2. **Labelling :** The label on the container states (1) the name of the product; (2) the total amount of active ingredient(s) in the container; (3) that the container should be shaken before each use; (4) a warning that the container is under pressure and that it must be kept away from heat and direct sunlight and must not be punctured, broken or incinerated even when apparently empty; (5) the statement—Warning 'Keep away from eyes', 'Keep away from children'.

In the case of metered-dose aerosols, the following additional information is stated; (1) the total number of metered doses available from the container; (2) the amount of active ingredient(s) released each time the valve is actuated.

Instruction leaflet should include (1) the directions for the correct use of the aerosol; (2) a warning that the container may explode, if punctured, exposed to heat or to direct sunlight, and (3) directions for the disposal of the used or partly-used container.

Amoxycillin for Oral Suspension

Amoxycillin Mixture

Category: Antibacterial.

Dose: The equivalent of 0.75 g to 4.5 g of amoxycillin daily, in divided doses.

Usual strengths: The equivalent of 125 mg; 250 mg of amoxycillin in 5 ml.

Standards: Amoxycillin for Oral Suspension is a mixture Amoxycillin Trihydrate with one or more suitable colouring, flavouring, sweetening, buffering and suspending agents and preservatives. When reconstituted as directed, it contains not less than 90.0 per cent and not more than 120.0 per cent of the stated amount of amoxycillin, $C_{16}H_{19}N_3O_5S$.

Identification : Complies with **Identification** test (B) described under Amoxycillin Trihydrate, using the following solutions. For solution (1) weigh a quantity of the mixture equivalent to 125 mg of amoxycillin and add 100 ml of *buffer solution pH 7.0*; solution (2) is a 0.14 per cent w/v solution of *amoxycillin trihydrate R.S.* in *buffer solution pH 7.0.*

pH : Between 5.0 and 7.5, determined on the suspension obtained by reconstituting as directed on the label of the container, Appendix 5.10.

Water : Not more than 3.0 per cent w/w, Appendix 3.3.25.

Assay : Prepare a suspension as directed on the label of the container, immediately before analysis and reserve a portion of it for the test for **Stability of suspension.**

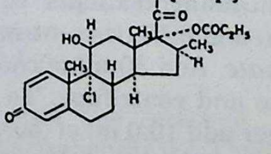
Weigh accurately a quantity equivalent to 0.15 g of amoxycillin, add sufficient *water* to produce 500.0 ml, shake for thirty minutes, filter, and complete the **Assay** described under Amoxycillin Trihydrate, beginning at the words "Transfer 10.0 ml...". Determine the weight per ml of the suspension, Appendix 5.19, and calculate the content of $C_{16}H_{19}N_3O_5S$ weight in volume.

Stability of suspension : Store the portion of the suspension reserved in the **Assay**, at the temperature and for the period stated on the label during which it may be expected to be satisfactory for use. Repeat the **Assay** on the stored suspension. The content of $C_{16}H_{19}N_3O_5S$ in the stored suspension is not less than 90.0 per cent of the content found in the freshly prepared suspension.

Storage: Store in tightly-closed containers in a cool place. The reconstituted suspension should be stored at the temperature stated on the label and used within the period indicated on the label.

Labelling : The label on the container states (1) the directions for preparing the suspension; (2) the strength as the equivalent weight of amoxycillin in a suitable dose-volume; (3) the temperature at which the contents and the prepared suspension are to be stored; (4) the period within which the prepared suspension should be used; (5) the date after which the contents are not intended to be used.

Beclomethasone Dipropionate



$C_{28}H_{37}ClO_7$ Mol. Wt. 521.05

Category : Adrenocortical steroid (topical anti-inflammatory).

Description : White to creamy-white powder; odourless.

Solubility : Practically insoluble in *water*; very soluble in *chloroform* and in *acetone*; sparingly soluble in *alcohol.*

Standards : Beclomethasone Dipropionate is 9α-chloro-11β, 17α, 21-trihydroxy-16β-methylpregna-l, 4-diene-3, 20-dione 17, 21-dipropionate. It contains not less than 96.0 per cent and not more than the equivalent of 104.0 per cent of $C_{28}H_{37}ClO_7$, calculated with reference to the dried substance.

Identification : (A) *The infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *beclomethasone dipropionate R.S.*, Appendix 5.15B.

(B) Complies with the test for *identification of steroids*, Appendix 3.3.11, using *solvent II* and *mobile phase D.*

(C) Carry out the *oxygen-flask method,* Appendix 3.3.6, on 25 mg using a mixture of 20 ml of *water* and 1 ml of *N sodium hydroxide* as the absorbing liquid. The liquid gives the reactions of *chlorides*, Appendix 3.1.

(D) Complies with the reaction for *acetyl groups*, Appendix 3.1; a blue colour appears slowly at the junction of the two liquids.

(E) It melts at about 212° with decomposition, Appendix 5.11.

Specific optical rotation : Between + 88° and + 94°, determined in a 1 per cent w/v solution in *dioxan,* Appendix 5.12.

Light absorption : *Extinction* of a 1-cm layer of a 0.0020 per cent w/v solution in *ethyl alcohol* at the maximum at about 238 nm, 0.57 to 0.60, Appendix 5.15A. Ratio of the *extinction* at the maximum at about 238 nm to that at 263 nm, 2.25 to 2.45.

Related foreign steroids : Complies with the test for *related foreign steroids, method B,* using as solution (3) a solution containing 0.030 per cent w/v of *beclomethasone 17-propionate R.S.* in a mixture of 9 volumes of *chloroform* and 1 volume of *methyl alcohol.*

Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.5 per cent, determined on 0.5 g by drying in an oven at 105°, Appendix 5.8.

Assay : Carry out the **Assay** described under Betamethasone, using *beclomethasone dipropionate R.S.* for preparing the *standard solution.*

Storage : Store in well-closed, light-resistant containers.

Carbimazole Tablets

Category : Thyroid Inhibitor.

Dose : Carbimazole 5 to 45 mg daily, in divided dose.

Usual strength : 5 mg.

Standards : Carbimazole Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of carbimazole, $C_7H_{10}N_2O_2S$. The tablets may be coated.

Identification : To a small quantity of the powdered tablets add one drop of *dilute potassium iodobismuthate solution*; a red colour is produced.

Methimazole : Comply with the test described under Carbimazole, using as solution (1) a solution prepared by shaking a quantity of the powdered tablets equivalent to 10 mg of Carbimazole with 2 ml of *chloroform* for five minutes and filtering.

Uniformity of content : Powder one tablet, add 300 ml of *water* warmed to a temperature not exceeding 35°, shake for a few minutes and add sufficient *water* to produce 500.0 ml. Filter and measure the extinction of a 1-cm layer of the resulting solution at the maximum at about 291 nm, Appendix 5.15A.

Calculate the content of $C_7H_{10}N_2O_2S$, taking 557 as the value of E (1 per cent, 1 cm) at about 291 nm.

Repeat the operation with a further nine tablets and calculate the average content of ten tablets. The content of each tablet is between 90 and 110 per cent of the average except that for one tablet the content may be between 85 and 115 per cent of the average.

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powdered tablets equivalent to 40 mg of Carbimazole, add 300 ml of *water* warmed to a temperature not exceeding 35°, shake for a few minutes and add sufficient *water* to produce 500 ml. Mix well and filter; dilute 50.0 ml of the filtrate to 500.0 ml with *water* and mix well. Measure the extinction of a 1-cm layer of the resulting solution at the maximum at about 291 nm, Appendix 5.15A. Calculate the content of $C_7H_{10}N_2O_2S$, taking 557 as the value of E (1 per cent, 1 cm) at the maximum at about 291 nm.

Storage : Store in well-closed containers, in a cool place.

Clonidine Injection

Clonidine Hydrochloride Injection

Category : Antihypertensive.

Dose : Clonidine Hydrochloride. By slow intravenous injection, 150 to 300 mg.

Usual strength : 150 µg in 1 ml.

Standards : Clonidine Injection is a sterile solution of Clonidine Hydrochloride in water for Injection. It contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of $C_9H_9Cl_2N_3.HCl$.

Identification : (A) Dilute a volume equivalent to 300 µg of Clonidine Hydrochloride to 5 ml with *0.0IN hydrochloric acid.* The light absorption, in the range 245 to 350 nm, of the resulting solution exhibits maxima at 272 nm and 279 nm and an inflection at 265 nm, Appendix 5.15A.

(B) To a volume equivalent to 150 µg of Clonidine Hydrochloride add 1 ml of a 10 per cent w/v solution of *ammonium reineckate* and keep aside for a few minutes; a pink precipitate is obtained.

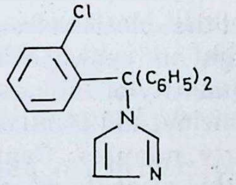
pH : Between 4.0 and 7.0, Appendix 5.10.

Other requirements : Complies with the requirements stated under Injections.

Assay : To a volume equivalent to 150 µg of Clonidine Hydrochloride add 25 ml of *citro-phosphate buffer, pH 7.6,* 5 ml of *water* and 1 ml of a solution containing 0.15 per cent w/v of *bromothymol blue* and 0.15 per cent w/v of anhydrous *sodium carbonate*. Add 30 ml of *chloroform,* shake for one minute and centrifuge. To 15.0 ml of the chloroform layer add 10.0 ml of *boric acid solution* and measure the *extinction* of the resulting solution at the maximum at about 420 nm, Appendix 5.15A, using as the blank, a solution of 10.0 ml of *boric acid solution* diluted to 25.0 ml with *chloroform.* Repeat the operation in the following manner. To 5.0 ml of a 0.003 per cent w/v solution of *Clonidine Hydrochloride R.S.* previously dried to constant weight at 105°, add 20 ml of *citrophosphate buffer, pH 7.6* and complete the procedure described above, beginning at the words " ... 5 ml of *water*...". Calculate the content of $C_9H_9Cl_2N_3.HCl$ from the *extinction* obtained and from the declared content of $C_9H_9Cl_2N_3.HCl$ in the *Clonidine Hydrochloride R.S.*

Storage : Store in single-dose containers.

Clotrimazole



$C_{22}H_{17}ClN_2$ Mol. Wt. 344.84

Category : Antifungal.

Description : White or pale yellow, crystalline powder.

Solubility : Practically insoluble in *water;* freely soluble in *methyl alcohol,* in *acetone,* in *chloroform* and in *alcohol.*

Standards : Clotrimazole is 1-[(2-chlorophenyl) diphenylmethyl]-1*H*-imidazole. It contains not less than 97.5 per cent and not more than the equivalent of 102.0 per cent of $C_{22}H_{17}ClN_2$, calculated with reference to the dried substance.

Identification : (A) The *infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *clotrimazole R. S.,* Appendix 5.15B.

(B) Carry out the method for *thin-layer chromatography,* Appendix 5.4.3, using *silica gel HF 254* as the coating substance and a mixture of 18 volumes of *xylene,* 2 volumes of *n-propyl alcohol* and 0.1 volume of *strong ammonia solution* as the mobile phase. Apply separately to the plate 10 µl of each of two solutions in *chloroform* containing (1) 2 per cent w/v of the substance being examined and (2) 2 per cent w/v of *clotrimazole R.S.* After removal of the plate, allow it to dry in air and examine under an ultra-violet lamp having a maximum output at about 254 nm. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

(C) It melts at about 148° with decomposition, Appendix 5.4.

Imidazole : Carry out the method for *thin-layer chromatography,* Appendix 5.4.3, using *silica gel G* as the coating substance and a mixture of 3 volumes of *methyl alcohol* and 2 volumes of *chloroform* as the mobile phase. Apply separately to the plate 5 µl of each of two solutions in *chloroform* containing (1) 10 per cent w/v of the substance being examined and (2) 0.05 per cent w/v of *imidazole R.S.* After removal of the plate, allow it to dry in air for five minutes, then place it in a closed container with a dish containing 100 g of *iodine* in a shallow layer and allow to stand for 60 minutes. Any spot in the chromatogram obtained with solution (1), other than the principal spot, is not more intense than the spot obtained in the chromatogram obtained with solution (2).

(2-chlorophenyl) diphenylmethanol : Carry out the method for *thin-layer chromatography,* Appendix 5.4.3, using *silica gel HF 254* as the coating substance and *isopropyl ether* saturated with *strong ammonia solution* as the mobile phase. Apply separately to the plate 10 µl of each of two solutions in *chloroform* containing (1) 20 per cent w/v of the substance being examined and (2) 0.1 per cent w/v of *(2-chlorophenyl) diphenylmethanol R.S.* After removal of the plate, allow it to dry in air and examine under an ultra-violet lamp having a maximum output at about 254 nm. Any spot in the chromatogram obtained with solution (1), other than the principal spot, is not more intense than the spot in the chromatogram obtained with solution (2).

Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105°, Appendix 5.8.

Assay : Weigh accurately about 0.17g, dissolve in 50 ml of *glacial acetic acid*, add 0.5 ml of α–*naphtholbenzein solution* and titrate with *0.1N perchloric acid* to a green end-point. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.03448 g of $C_{22}H_{17}ClN_2$.

Storage : Store in tightly-closed, light-resistant containers.

Colchicine Tablets

Category : Gout Suppressant.

Dose : Colchicine. Initial dose 1 mg; subsequent doses, 0.5 mg every two hours.

Usual strengths : 0.25 mg; 0.5 mg.

Standards : Colchicine Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of Colchicine, $C_{22}H_{25}NO_6$.

Indentification : (A) To a quantity of the powdered tablets equivalent to 10 mg of Colchicine add 20 ml of *water* and mix well. Filter into a separating funnel and extract with 30 ml of *chloroform*. Evaporate the chloroform extract to dryness using moderate heat. The *infra-red absorption spectrum* of the residue exhibits maxima which are only at the same wavelength as, and have similar relative intensities to, those in the spectrum of *colchicine R.S.*, Appendix 5.15B.

(B) To a quantity of the powdered tablets equivalent to 1 mg of Colchicine add 0.2 ml of *sulphuric acid* and mix; a yellow colour is produced. On adding a drop of *nitric acid* the colour changes to greenish-blue, then reddish and finally almost colourless. On the addition of an excess of *sodium hydroxide solution* the colour changes to red.

Related substances : Comply with the test described under Colchicine, using the following solutions. For solution (1) extract a quantity of the powdered tablets equivalent to 5 mg of Colchicine with 5 ml of *chloroform*, filter, and evaporate the filtrate to dryness in a current of air. Dissolve the residue as completely as possible in 0.1 ml of *alcohol*, centrifuge and use the supernatant liquid. For solution (2) dilute 1 volume of solution (1) to 20 volumes with *alcohol*.

Uniformity of content : Protect the solutions from light throughout the test. Crush one tablet and transfer to a centrifuge tube with the aid of 10 ml of *ethyl alcohol*. Shake for thirty minutes, centrifuge and wash the residue with *ethyl alcohol*. Combine the extract and washings and add sufficient *ethyl alcohol* to produce a 0.001 per cent w/v solution. Measure the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 350 nm, Appendix 5.15A. Calculate the content of $C_{22}H_{25}NO_6$, taking 425 as the value of E (1 per cent, 1 cm) at the maximum at about 350 nm.

Repeat the operation using a further nine tablets and calculate the average content of the ten tablets. The content of each tablet is between 85 and 115 per cent of the average except that for one tablet the content may be between 80 and 120 per cent of the average.

Other requirements : Comply with the requirements stated under Tablets.

Assay : Protect the solutions from light throughout the test. Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 0.5 mg of Colchicine, add 10 ml of *ethyl alcohol* and shake for thirty minutes. Centrifuge, wash the residue with *ethyl alcohol* and mix the extract and washings in a 50-ml volumetric flask. Dilute to volume with *ethyl alcohol* and mix. Measure the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 350 nm, Appendix 5.15A. Calculate the content of $C_{22}H_{25}NO_6$, taking 425 as the value of E (1 per cent, 1 cm) at the maximum at about 350 nm.

Storage : Store in tightly-closed, light- resistant container.

Dextrin

Category : Pharmaceutical aid (Tablet excipient)

Description : White or pale yellow amorphous powder; odour, slight and characteristic.

Solubility : Slowly soluble in cold *water;* very soluble in boiling *water* forming a mucilaginous solution; insoluble in *alcohol* and in *solvent ether*.

Standards : Dextrin is starch, partially hydrolysed by heat with or without the aid of suitable acids and buffers.

Microscopical characteristics — Granules have similar appearance to the starch from which the dextrin has been prepared. In dextrin from maize starch many of the granules show concentric striations and in dextrin prepared from potato starch concentric striations are not clearly visible, the hilum may be bicleft and some of the granules may be distorted.

Identification : (A) Boil 1 g in 50 ml of *water*, cool, add a drop of *iodine solution* and mix; a purple colour is produced.

(B) To 5 ml of the suspension produced in **Identification** test (A) add 2 ml of *2N sodium hydroxide*, mix, add dropwise with stirring 0.5 ml of *copper sulphate solution* and boil; a red precipitate is produced.

Acidity : Add 10 g to 100 ml of *alcohol (70 per cent)*, previously neutralised to *phenolphthalein solution*, shake for one hour, filter and titrate 50 ml of the filtrate with *0.1N sodium hydroxide* using *phenolphthalein solution* as indicator. Not more than 1.0 ml of *0.1N sodium hydroxide* is required.

Chloride : Dissolve 1.75 g in 50 ml of boiling *water*, cool, dilute to 100 ml with *water*, and filter; 10 ml of the filtrate complies with the *limit test for chlorides*, Appendix 3.2.2.

Sulphate : Dissolve 3.0 g in 50 ml of boiling *water*, cool, dilute to 100 ml with *water* and filter; 10 ml of the filtrate complies with the *limit test for sulphates*, Appendix 3.2.8.

Heavy metals : Not more than 40 parts per million, determined on 0.5 g by method A, Appendix 3.2.4.

Alcohol-soluble substances : Not more than 1 per cent, determined by the following method.

Boil under reflux 1.0 g with 20 ml of *alcohol* for five minutes and filter while hot. Evaporate 10 ml of the filtrate on a water-bath and dry the residue at 105°.

Reducing sugars : Not more than 10 per cent, calculated as dextrose, $C_6H_{12}O_6$ and determined by the following method.

Weigh accurately a quantity equivalent to 2 g of the dried substance, add 100 ml of *water*, and shake for thirty minutes, dilute to 200.0 ml with *water* and filter. To 10.0 ml of *alkaline solution of cupric tartrate* add 20.0 ml of the filtrate, mix and heat at a rate such that the solution is brought to boil in three minutes. Boil for a further two minutes and cool quickly. Add 5 ml of a 30 per cent w/v solution of *potassium iodide* and 10 ml of *N sulphuric acid*, mix, and titrate immediately with *0.1N sodium thiosulphate* using *starch solution*, added towards the end of the titration, as indicator. Repeat the procedure using 20.0 ml of a 0.1 per cent w/v solution of *dextrose* in place of the filtrate, beginning at the words "To 10.0 ml of ...". Perform a blank titration using 20.0 ml of *water* in place of 20 ml of the sample filtrate and make any necessary correction. The titre obtained with the sample filtrate is not greater than the titre obtained with the dextrose solution.

Ash : Not more than 1.0 per cent, Appendix 3.3.22.

Loss on drying : Not more than 12.0 per cent, determined on 1 g by drying in an oven at 110°, Appendix 5.8.

Storage : Store in well-closed containers, protected from moisture.

Dextropropoxyphene Capsules

Propoxyphene Capsules

Category : Analgesic.

Dose : Upto the equivalent of 240 mg of dextropropoxyphene daily, in divided doses.

Usual strength : The equivalent of 60 mg of dextropropoxyphene.

Standards : Dextropropoxyphene Capsules contain a quantity of Dextropropoxyphene Hydrochloride or Dextropropoxyphene Napsylate equivalent to not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of dextropropoxyphene, $C_{22}H_{29}NO_2$.

Identification : Shake a quantity of the contents of the capsules equivalent to 0.15 g of dextropropoxyphene with 5 ml of chloroform and filter. The filtrate complies with the following tests: (A), (B) and (C).

(A) The infra-red absorption spectrum exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *dextropropoxyphene hydrochloride R.S.* or of *dextropropoxyphene napsylate R.S.,* Appendix 5.15B.

(B) Evaporate 0.05 ml in a dish and streak the spot with *sulphuric acid* containing 0.05 ml of *formaldehyde solution* per ml; a purple colour is produced.

(C) Evaporate 0.4 ml on a piece of filter paper and burn the residue by the *oxygen-flask method,* Appendix 3.3.6, using 5 ml of *dilute sodium hydroxide solution* as the absorbing liquid. When the process is complete, dilute the liquid to 25 ml with *water.* To 5 ml of the solution so obtained, add 1 ml of *strong hydrogen peroxide solution,* 1 ml of *N hydrochloric acid,* mix well, and add 0.05 ml of *barium chloride solution;* a turbidity is produced (for capsules containing dextropropoxyphene napsylate only).

(D) To a quantity of the contents of the capsules equivalent to about 120 mg of dextropropoxyphene and 20 ml of *water,* 5 ml of *N sodium hydroxide* and swirl for three minutes. Extract with 10 ml of *chloroform* and allow the layers to separate. Run off the chloroforum layer and filter a portion of the extracted alkaline water mixture. To 5 ml of the clear filtrate add enough *dilute nitric acid* to make the solution acid to litmus and add ten drops of *silver nitrate solution;* a white precipitate is formed and it is soluble in an excess of *dilute ammonia solution* (for capsules containing dextropropoxyphene hydrochloride only).

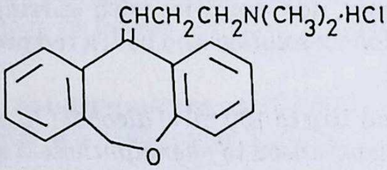
Other requirements : Comply with the requirements stated under Capsules.

Assay : To a quantity of the mixed contents of 20 capsules equivalent to 0.5 g of dextropropoxyphene add 25 ml of *chloroform,* stir well and filter through a plug of cotton wool, washing the flask and filter with small quantities of *chloroform.* Add to the combined filtrate a mixture of 50 ml of *water* and 5 ml of *sodium hydroxide solution,* shake, allow the layers to separate and wash the chloroform extract with 25 ml of *water.* Extract the aqueous layer with five further quantities, each of 25 ml, of *chloroform,* washing each extract with the 25 ml of *water* and adding it to the original extract. Dry the combined extracts with *anhydrous sodium sulphate,* evaporate to about 3 ml on a water-bath in a current of air, and further evaporate to dryness at room temperature. To the residue add 20 ml of *anhydrous glacial acetic acid* and titrate with *0.1N perchloric acid,* using *crystal violet solution* as indicator. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.03395 g of $C_{22}H_{29}NO_2$.

Storage : Store in tightly-closed containers.

Labelling : The label on the container states (1) whether the capsules contain Dextropropoxyphene Hydrochloride or Dextropropoxyphene Napsylate; (2) the active ingredient in terms of the equivalent amount of dextropropoxyphene.

Doxepin Hydrochloride



$C_{19}H_{21}NO,HCl$ Mol. Wt. 315.84

Category : Antidepressant

Dose : The equivalent of 75 to 150 mg of doxepin daily.

Description : White, crystalline powder; odour slight and amine-like.

Solubility : Freely soluble in *water,* in *alcohol* and in *chloroform.*

Standards : Doxepin Hydrochloride is 3-(6*H*-*dibenz* [*b*, *e*]oxepin-11-ylidene) propyldimethylammonium chloride; it consists of a mixture of *Z* and *E* isomers. It contains not less than 85.0 per cent and not more than the equivalent of 90.0 per cent of doxepin, $C_{19}H_{21}NO$, calculated with reference to the dried substance.

Identification : (A) The *infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *doxepin hydrochloride R.S.,* Appendix 5.15B.

(B) The light absorption, in the range 230 to 350 nm, of a 1-cm layer of a 0.004 per cent w/v solution in *0.01N methanolic hydrochloric acid* exhibits a maximum only at 297 nm, *extinction* at 297 nm, about 0.52, Appendix 5.15A.

(C) Dissolve 5 mg in 2 ml of *nitric acid;* a red colour is produced.

(D) A solution (1 in 20) gives the reactions of *chlorides,* Appendix 3.1.

Melting range : Between 185° and 191°, Appendix 5.11.

Cis-isomer: Between 13.0 and 18.5 per cent, determined by the following method. Carry out the method for *gas chromatography,* Appendix 5.4.1, using two solutions in *methyl alcohol* containing (1) 0.5 per cent w/v of *doxepin hydrochloride R.S.* and (2) 0.5 per cent w/v of the substance being examined. Carry out the chromatographic procedure using (a) a glass column 1.5 m long and 4 mm internal diameter, packed with 3 per cent w/w of a cyanopropylmethylphenylmethyl silicone fluid such as OV225 on acid-washed, silanised diatomaceous earth (100 to 200 mesh) and maintained at 200°; (b) nitrogen as the carrier gas, and (c) a flame ionisation detector. Measure the areas or heights respectively of the peaks of cis-doxepin which immediately precede and are separate from the trans-isomer which forms the main peak, in the chromatogram obtained with the substance being examined and in the chromatogram obtained with *doxepin hydrochloride R.S.* Calculate the content of the cis-isomer in the substance being examined, from the declared content of the cis-isomer in the doxepin hydrochloride R.S.

Heavy metals : Not more than 20 parts per million, determined by method B using 1 g, Appendix 3.2.4.

Sulphated ash : Not more than 0.2 per cent, Appendix 3.2.7.

Loss on drying : Not more than 1.0 per cent, determined on 1.0 g by drying in an oven at 105°, Appendix 5.8.

Assay : Weigh accurately about 0.6 g and dissolve in 100 ml of *acetone.* Add 15 ml of *mercuric acetate solution* and titrate with *0.1N perchloric acid,* using 3 ml of a saturated solution of *methyl orange* in *acetone* as indicator. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* in equivalent to 0.02794 g of $C_{19}H_{21}NO$.

Storage : Store in well-closed, light-resistant containers.

Doxepin Capsules

Doxepin Hydrochloride Capsules

Category : Antidepressant.

Dose : The equivalent to 75 to 150 mg of doxepin daily.

Usual strengths : Capsules containing in each, the equivalent to 25 mg, 50 mg and 75 mg of doxepin.

Standards : Doxepin Capsules contain a quantity of Doxepin Hydrochloride equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of doxepin, $C_{19}H_{21}NO$.

Identification : Wash a quantity of the contents of the capsules equivalent to 0.1 g of doxepin with three quantities, each of 5 ml, of *light petroleum (boiling range, 40° to 60°).* Dry the residue in air and then exract with three quantities, each of 10 ml, of *chloroform,* evaporate the combined extracts to dryness and dry the residue at 105°. The dried residue complies with **Indentification** tests (A) to (D), described under Doxepin Hydrochloride.

Cis-isomer : Comply with the test described under Doxepin Hydrochloride, using for solution (2) the supernatant liquid obtained by extracting a quantity of the mixed contents of 20 capsules equivalent to 25 mg of doxepin with 5 ml of *methyl alcohol* and centrifuging.

Other requirements : Comply with the requirements stated under Capsules.

Assay : Weigh accurately a quantity of the mixed contents of 20 capsules equivalent to about 30 mg of doxepin, add 50 ml of *0.01N methanolic hydrochloric acid,* shake for thirty minutes and add sufficient *0.01N methanolic hydrochloric acid,* to produce 100.0 ml. Centrifuge 40 ml and dilute 10.0 ml of the clear supernatant liquid to 100.0 ml with *0.01N methanolic hydrochloric acid.* Measure the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 297 nm, Appendix 5.15A. Calculate the content of doxepin, $C_{19}H_{21}NO$. taking 150 as the value of E (1 per cent, 1 cm) at the maximum at about 297 nm.

Storage : Store in tightly-closed containers.

Labelling : The label on the container states the strength in terms of the equivalent amount of doxepin.

Ethosuximide Capsules

Category : Anticonvulsant.

Dose : Ethosuximide, 500 mg daily, in divided doses increasing to 2 g, as necessary.

Usual strengths : 250 mg.

Standards : Ethosuximide Capsules contain not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of Ethosuximide, $C_7H_{11}NO_2$.

Identification : (A) Place a portion of the contents of the capsules equivalent to about 300 mg of Ethosuximide, in a separator containing 50 ml of *solvent ether,* shake with three quantities, each 10 ml, of *water* and discard the aqueous extracts. Add about 5 g of *anhydrous sodium sulphate,* swirl for three minutes and filter through a plug of cotton wool previously washed with *solvent ether.* Evaporate the ether extract at room temperature with the aid of a current of air, to dryness. Dissolve the residue in 5 ml of *chloroform.* The *infra-red absorption spectrum* of the chloroform solution exhibits maxima which are at the same wavelengths as, and have similar relative intensities to, those in the spectrum obtained with a chloroform solution of *ethosuximide R.S.* treated in a similar manner, Appendix 5.15B.

(B) Heat a quantity of the contents of the capsules equivalent to 0.1 g of Ethosuximide with 0.2 g of *resorcinol* and 0.1 ml of *sulphuric acid* at 140° for five minutes, add 5 ml of *water,* make alkaline with *sodium hydroxide solution* and pour a few drops into a large volume of *water;* a bright green fluorescence is obtained.

(C) Shake a quantity of the contents of the capsules equivalent to 0.25 g of Ethosuximide with 80 ml of *alcohol* for a few minutes, add sufficient *alcohol* to produce 100.0 ml, mix, and filter. Dilute 20.0 ml of the filtrate to 100.0 ml with *alcohol. Extinction* of a 1-cm layer of the resulting solution at the maximum at about 248 nm, about 0.43, Appendix 5.15A.

Other requirements : Comply with the requirements stated under Capsules.

Assay : Weigh accurately a quantity of the contents of the capsules equivalent to 0.2 g of Exthosuximide and dissolve in 30 ml of *dimethylformamide.* Add two drops of a 0.1 per cent w/v solution of *azo violet* in *dimethylformamide* and titrate with *0.1N sodium methoxide* to a deep blue end-point, taking pracautions to prevent absorption of atmospheric carbon dioxide. Perform a blank determination and make any necessary correction. Each ml of *0.1N sodium methoxide* is equivalent to 0.01412 g of $C_7H_{11}NO_2$.

Storage : Store in tightly-closed containers.

Glycine

Aminoacetic acid

$H_2NCH_2CO_2H$

$C_2H_5NO_2$ Mol. Wt. 75.07

Category : Pharmaceutical aid.

Description : White, crystalline powder; odourless.

Solubility : Freely soluble in *water;* very slightly soluble in *alcohol* and in *solvent ether.*

Standards : Glycine contains not less than 99.0 per cent and not more than the equivalent of 101.5 per cent of $C_2H_5NO_2$, calculated with reference to the dried substance.

Identification : (A) *infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *glycine R. S.,* Appendix 5.15B.

(B) Dissolve 1 g in 10 ml of *water;* to 5 ml add 5 drops of *2N hydrochloric acid* and 1 ml of *sodium nitrite solution;* a vigorous evolution of colourless gas is produced.

(C) To 2 ml of the solution obtained in **Identification** test (B) add 1 ml of *ferric chloride solution;* a red colour is produced which is discharged by an excess of *hydrochloric acid* and is restored by an excess of *strong ammonia solution.*

(D) To 2 ml of the solution obtained in **Identification** test (B) add one drop of *liquefied phenol,* shake, and add carefully without shaking 5 ml of *dilute sodium hypochlorite solution;* a blue colour is produced.

pH : Between 5.9 and 6.3, determined in a 5 per cent w/v solution, Appendix 5.10.

Ammonium compounds : Not more than 20 parts per million, determined by the following method. Dissolve 0.50 g in 70 ml of *water* in an ammonia distillation apparatus, add 25 ml of *nitrogen-free sodium hydroxide solution,* and distil into 2 ml of a saturated solution of *boric acid* until a volume of 50 ml is obtained. Add 2 ml of *ammonia-free sodium hydroxide solution* and 2 ml of alkaline *potassium mercuri-iodide solution.* Any colour produced is not more intense than that obtained by treating 70 ml of *water* containing 1 ml of *ammonia standard solution (10 ppm NH_4)* in the same way, beginning with the words "add 25 ml ...".

Chloride : 0.2 g complies with the *limit test for chlorides,* Appendix 3.2.2.

Heavy metals : Not more than 10 parts per million, determined on 1 g by method A, Appendix 3.2.4.

Hydrolysable substances : Dissolve 2 g in 20 ml of *water.* Boil 10 ml of the solution for one minute and set aside for two hours; the solution appears as clear and as mobile as 10 ml of the same solution that has not been boiled.

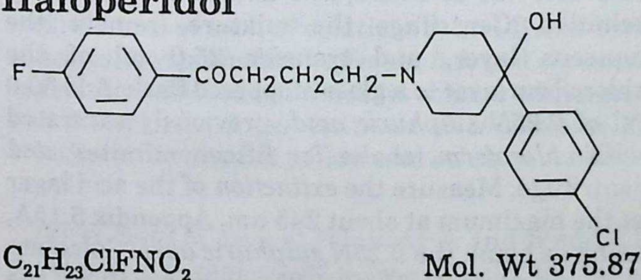
Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.2 per cent, determined on 1 g by drying in an oven at 105°, Appendix 5.8.

Assay : Weigh accurately about 0.15 g and dissolve in 50 ml of *anhydrous glacial acetic acid.* Add one drop of *crystal violet solution* and titrate with *0.1N perchloric acid* to a green end-point. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.007507 g of $C_2H_5NO_2$.

Storage : Store in well-closed containers.

Haloperidol



$C_{21}H_{23}ClFNO_2$ Mol. Wt 375.87

Categoroy : Antipsychotic (Tranquilliser).

Dose : 3 to 9 mg daily, in divided doses. By intramuscular or intravenous injection, 5 to 10 mg.

Description : White to faintly yellowish, amorphous or microcrystalline powder; odourless.

Solubility : Practically insoluble in *water;* sparingly soluble in *alcohol;* slightly soluble in *solvent ether;* soluble in *chloroform.*

Standards : Haloperidol is 8-[4-(4-chlorophenyl)-4-hydroxypiperidino]-4-fluorobutyrophenone. It contains not less than 98.0 per cent and not more than 101.0 per cent of $C_{21}H_{23}ClFNO_2$, calculated with reference to the dried substance.

Identification : (A) the *infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *haloperidol R.S.,* Appendix 5.15B.

(B) Carry out the *oxygen-flask method,* Appendix 3.3.6, using 20 mg of the substance being examined and 5 ml of *1.25N sodium hydroxide* as the absorbing liquid. When the process is complete, dilute to 10 ml with *water;* the resulting solution complies with the following tests:

(a) Add 0.1 ml to a mixture of 0.1 ml of freshly prepared *alizarin red S solution* and 0.1 ml of *zirconyl nitrate solution;* the red colour becomes clear yellow.

(b) Acidify 5 ml with *N sulphuric acid* and boil gently for 2 minutes; the solution gives the rections of *chlorides,* Appendix 3.1.

Melting range : Between 147° and 152°, determined on the material dried 'in vacuo' at 60° for three hours, Appendix 5.11.

Light absorption : *Extinction* of a 1-cm layer of a 0.0015 per cent w/v solution in a mixture of 10 volumes of *0.1N hydrochloric acid* and 90 volumes of *methyl alcohol* at the maximum at about 245 nm, about 0.49 to 0.53, Appendix 5.15A.

Related substances : Carry out the method for *thin-layer chromatography,* Appendix 5.4.3, using silica gel G as coating substance and a mixture of 80 volumes of *chloroform,* 10 volumes of *glacial acetic acid* and 10 volumes of *methyl alcohol* as the mobile phase. Apply separately to the plate 10 µl of each of three solutions in *chloroform* containing (1) 1.0 per cent w/v of the substance being examined, (2), 0.0050 per cent w/v of the substance being examined, (3) 0.010 per cent w/v of the substance being examined. After removal of the plate, allow it to dry in air and expose to the vapour of iodine for one hour. Any spot in the chromatogram obtained with solution (1), other than the principal spot, is not more intense than the spot in the chromatogram obtained with solution (2), except that one spot may be not more intense than the spot in the chromatogram obtained with solution (3).

Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.5 per cent, determined on 1 g by drying 'in vacuo' at 60° for three hours, Appendix 5.8.

Assay : Weigh accurately about 0.2 g, dissolve in 25 ml of *glacial acetic acid,* add three drops of *1-naphtholbenzein solution* and titrate with *0.05N perchloric acid.* Perform a blank determination and make any necessary correction. Each ml of *0.05N perchloric acid* is equivalent to 0.01879 g of $C_{21}H_{23}ClFNO_2$.

Storage : Store in tightly-closed, light-resistant containers.

Haloperidol Tablets

Category : Antipsychotic (tranquilliser).

Dose : Haloperidol, 3 to 9 mg daily, in divided doses.

Usual strengths : 0.25 mg; 0.5 mg; 5 mg and 10 mg.

Standards : Haloperidol Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of Haloperidol, $C_{21}H_{23}ClFNO_2$.

Identification : (A) To a quantity of the powdered tablets equivalent to 10 mg of Haloperidol add 10 ml of *water* and 1 ml of *N sodium hydroxide* and extract with 10 ml of *solvent ether.* Filter the ether extract, evaporate the filtrate to dryness and dry the residue at 60° 'under vacuo'. The *infra-red absorption spectrum* of the dried residue exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in spectrum of *haloperidol R.S.,* Appendix 5.15B.

(B) The light absorption, in the range 230 to 350 nm, of the solution obtained in the **Assay** exhibits a maximum only at 245 nm, Appendix 5.15A.

Uniformity of content : Powder one tablet, triturate thoroughly with 5 ml of a mixture of 1 volume of *0.1N hydrochloric acid* and 9 volumes of *methyl alcohol* and centrifuge. Repeat the extraction with three further quantities, each of 5 ml, of the same mixture. Dilute the combined extracts to 25.0 ml with the acid-methyl alcohol mixture. If necessary, dilute a suitable aliquot with the acid-methyl alcohol mixture to produce a solution containing about 10 µg of Haloperidol per ml. Measure the *extinction* of the resulting solution at the maximum at about 245 nm, Appendix 5.15A, using as blank the acid-methyl alcohol mixture. Calculate the content of $C_{21}H_{23}ClFNO_2$, taking 340 as the value of E (1 per cent, 1 cm) at the maximum at about 245 nm.

Repeat the operation with a further nine tablets and calculate the average content of the ten tablets. The content of each tablet is between 85 and 115 per cent of the average except that for one tablet the content may be between 80 and 120 per cent of the average.

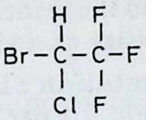
Related substances : Comply with the test described under Haloperidol, using the following solutions. For solution (1) shake a quantity of the powdered tablets equivalent to 10 mg of Haloperidol with 10 ml of *chloroform*, filter, evaporate the filtrate to dryness and dissolve the residue in 1 ml of *chloroform*; for solution (2) dilute 1 volume of solution (1) to 200 volumes with *chloroform*; for solution (3) dilute 1 volume of solution (1) to 100 volumes with *chloroform.*

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 1.5 mg of Haloperidol, and transfer to a glass-stoppered flask. Add 25 ml of *0.1N sodium hydroxide* and 50.0 ml of *chloroform* and shake for thirty minutes. Centrifuge the mixture, remove the aqueous layer, and transfer 25.0 ml of the chloroform layer to a glass-stoppered flask. Add 50.0 ml of *0.25N sulphuric acid*, previously saturated with *chloroform,* shake for fifteen minutes, and centrifuge. Measure the *extinction* of the acid layer at the maximum at about 245 nm, Appendix 5.15A, using as blank the *0.25N sulphuric acid.* Calculate the content of $C_{21}H_{23}ClFNO_2$, taking 340 as the value of E (1 per cent, 1 cm) at the maximum at about 245 nm.

Storage : Store in tightly-closed, light-resistant containers.

Halothane



$C_2HBrClF_3$ Mol. Wt. 197.38

Category : Anaesthetic, General.

Description : Clear, colourless, mobile, dense liquid; odour, characteristic.

Solubility : Slightly soluble in *water;* miscible with *ethyl alcohol,* with *solvent ether,* with *chloroform,* with *trichloroethylene* and with fixed and essential oils.

Standards : Halothane is 2-bromo-2-chloro-1, 1,1-trifluoroethane. It contains 0.01 per cent w/v of Thymol.

Identification : To 0.1 ml add 2 ml of *t-butyl alcohol,* 1 ml of *copper edetate solution,* 0.5 ml of *strong ammonia solution* and 2 ml of *hydrogen peroxide solution* (solution A). Simultaneously prepare a solution in the same way omitting the substance being examined (solution B). Warm both solutions in a water-bath at 50° for fifteen minutes, cool, add 0.3 ml of *glacial acetic acid* to each and carry out the following tests:

(1) To 1 ml of each of the solution A and B add 0.5 ml of a mixture of equal volumes of freshly prepared *alizarin red S solution* and *zirconyl nitrate solution.* Solution B is coloured red and solution A is yellow.

(2) To 1 ml of each of solutions A and B add 1 ml of *neutralised phthalate buffer pH 5.2,* 1 ml of *phenol red solution* diluted ten times its volume with *water* and 0.1 ml of a 2 per cent w/v of *chloramine T;* solution B is coloured yellow and solution A bluish purple.

(3) To 2 ml of each of solutions A and B add 0.5 ml of a 25 per cent v/v of *sulphuric acid,* 0.5 ml of *acetone,* and 0.2 ml of a 5 per cent w/v solution of *potassium bromate* and shake. Warm the solutions in a water-bath at 50° for two minutes, cool, add 0.5 ml of a 50 per cent v/v solution of *nitric acid* and 0.5 ml of *0.1N silver nitrate;* solution B remains clear and solution A is cloudy and forms a white precipitate after a few minutes.

Specific gravity : Between 1.872 and 1.877 at 20°, Appendix 5.19.

Distilling range : Between 49° and 51°, Appendix 5.3.

Acidity or Alkalinity : Shake 20 ml with 20 ml of *carbon dioxide-free water* for three minutes. Separate the aqueous layer and add 0.1 ml of *bromocresol purple solution;* not more than 0.1 ml of *0.01N sodium hydroxide* or 0.6 ml of *0.01N hydrochloric acid* is required to change the colour of the solution.

Halide : Shake 10 ml with 20 ml of *carbon dioxide-free water* for three minutes. To 5 ml of the aqueous layer add 5 ml of *water,* 0.05 ml of *nitric acid* and 0.20 ml of *0.25N silver nitrate;* no opalescence is produced.

Free halogens : To 10 ml of the aqueous layer produced in the test for **Halide** add 1 ml of *potassium iodide* and *starch solution*; no blue colour is produced.

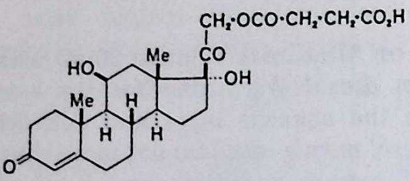
Non-volatile matter : Evaporate 50 ml in a tared dish on a water-bath to dryness, and dry the residue at 100° to 105° for two hours; the residue weighs not more than 1 mg.

Thymol : Weigh accurately about 2 ml and transfer to a 100-ml flask containing 5 ml of *0.25N sodium hydroxide,* and mix with gentle swirling. Evaporate the halothane under a stream of nitrogen, add 10 ml of *alkaline borate buffer solution pH 8.0* and 1 ml of a freshly prepared 0.4 per cent w/v solution of *2, 6-dibromoquinone chlorimide* in *ethyl alcohol.* Swirl gently and allow to stand for fifteen minutes, accurately timed, add 3 ml of *0.25 N sodium hydroxide* and add *water* to volume and mix. Measure the *extinction* of the resulting solution at the maximum at about 590 nm, Appendix 5.15A, using as blank a solution prepared in the same manner omitting the substance being examined and using 5 ml of *0.25 N sodium hydroxide* and beginning at the words "add 10 ml of *alkaline borate buffer solution pH 8.0...*". Calculate the thymol content from the *extinction* obtained by repeating the operation using a solution in *0.25N sodium hydroxide* containing 0.1 mg per ml of *thymol.*

Storage : Store in tightly-closed, light-resistant containers in a cool place and avoid exposure to excessive heat.

Hydrocortisone Hydrogen Succinate

Hydrocortisone Hemisuccinate; Cortisol Hemisuccinate



$C_{25}H_{34}O_8$ Mol. Wt. 462.54

Category : Adrenocortical steroid.

Description : White or almost white, crystalline powder; odourless.

Solubility : Practically insoluble in *water;* soluble in *sodium bicarbonate solution;* sparingly soluble in *alcohol;* freely soluble in *ethyl alcohol.*

Standards : Hydrocortisone Hydrogen Succinate is 11β, 17α, 21-trihydroxypregn-4 ene-3, 20-dione 21-hydrogen succinate. It contains not less than 97.0 per cent not more than the equivalent of 103.0 per cent of $C_{25}H_{34}O_8$, calculated with reference to the dried substance.

Identification : (A) The *infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *hydrocortisone hydrogen succinate R.S.*, Appendix 5.15B.

(B) Carry out the method for *thin-layer chromatography,* Appendix 5.4.3., using *silica gel G* as the coating substance and a freshly prepared mixture of 3 volumes of *n-butyl alcohol,* 1 volume of *acetic anhydride,* and 1 volume of *water* as the mobile phase. Apply separately to the plate 2μl of each of two solutions in *methyl alcohol* containing (1) 0.25 per cent w/v of the substance being examined and (2) 0.25 per cent w/v of *hydrocortisone hydrogen succinate R.S.* At the third point, apply 2μl of a mixture of equal volumes of solutions (1) and (2). After removal of the plate, allow it to dry in air until the solvents have evaporated, spray with a 10 per cent v/v solution of *sulphuric acid* in *alcohol,* heat at 120° for ten minutes, allow to cool, and examine under an ultra-violet lamp having a maximum output at 366 nm. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2) and the principal spot in the third chromatogram appears as a single compact spot.

Specific optical rotation : Between + 124° and + 134°, determined in a 1 per cent w/v solution in *acetone,* Appendix 5.12.

Acidity : Dissolve a quantity equivalent to 1.0 g of the dried substance in 20 ml of *ethyl alcohol,* previously neutralised to *phenolphthalein solution,* and titrate with *0.1N sodium hydroxide* using *phenolphthalein solution* as indicator; not less than 20.9 ml and not more than 22.3 ml of *0.1N sodium hydroxide* are required.

Related foreign steroids : Carry out the test for *related foreign steroids, method B,* Appendix 3.3.12 using solutions in a mixture of equal volumes of *chloroform* and *methyl alcohol* containing (1) 1.5 per cent w/v of the substance being examined, (2) 1.5 per cent w/v of *hydrocortisone hydrogen succinate R.S.* and (3) 0.030 per cent w/v of each of *hydrocortisone R.S.* and *hydrocortisone acetate R.S.* Any spot in the chromatogram obtained with solution (1), other than the principal spot, is less intense than the proximate spot in the chromatogram obtained with solution (3).

Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 4.0 per cent, determined on 1.0 g by drying in an oven for 3 hours at 105°, Appendix 5.8.

Assay : Weigh accurately about 15 mg, dissolve in sufficient *ethyl alcohol* to produce 100.0 ml, dilute 5.0 ml to 50.0 ml with *ethyl alcohol* and measure the *extinction* of the resulting solution at the maximum at about 240 nm, Appendix 5.15A. Calculate the content of $C_{25}H_{34}O_8$, taking 345 as the value of E (1 per cent, 1 cm) at the maximum at about 240 nm.

Storage : Store in tightly-closed, light-resistant containers.

Isoxsuprine Injection

Isoxsuprine Hydrochloride Injection

Category : Vasodilator.

Dose : Isoxsuprine Hydrochloride. In premature labour, by intravenous infusion, the equivalent of 0.2 mg to 0.5 mg per minute for

12 hours according to the response of the patient, followed by 10 mg intramuscularly every three hours.

Usual strength : 5 mg per ml.

Standards : Isoxsuprine Injection is a sterile solution of Isoxsuprine Hydrochloride in Water for Injection. It contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of $C_{18}H_{23}NO_3$, HCl.

Identification : (A) To a volume equivalent to 50 mg of Isoxsuprine Hydrochloride add 20 ml of *water* and 10 ml of *ammonia buffer pH 10.0* and extract with three quantities, each of 15 ml, of *methylene chloride.* Shake the combined extracts with 5 g of *anhydrous sodium sulphate,* filter and evaporate the filtrate to dryness. Dissolve the residue in 5 ml of *0.1N methanolic hydrochloric acid* and evaporate. Dissolve the residue in 5 ml of *methyl alcohol,* evaporate to dryness, redissolve the residue in 2 ml of *methyl alcohol,* add 15 ml of *methylene chloride,* again evaporate to dryness, and dry the residue at 60° 'in vacuo' for one hour. The *infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in spectrum of *isoxsuprine hydrochloride R.S.,* Appendix 5.15B.

(B) The light absorption, in the range 230 to 350 nm, of the solution obtained in the **Assay** exhibits maxima at 269 nm and at 274 nm, Appendix 5.15A.

pH : Between 4.9 and 6.0, Appendix 5.10.

Pyrogens : Complies with the *test for pyrogens,* Appendix 2.36, using 5 mg per kg of the rabbit's weight and a solution containing 5 mg per ml.

Other requirements : Complies with the requirements stated under Injections.

Assay : Measure accurately a volume equivalent to 50 mg of Isoxsuprine Hydrochloride and add sufficient *0.1N hydrochloric acid* to produce 100.0 ml. Dilute 10.0 ml to 100.0 ml with the same solvent and measure the *extinction* of the resulting solution at the maximum at about 274 nm, Appendix 5.15A. Calculate the content of $C_{18}H_{23}NO_3$, HCl, taking 73 as the value of E (1 per cent, 1 cm) at the maximum at about 274 nm.

Storage : Store in single-dose or multiple-dose containers.

Isoxsuprine Tablets

Isoxsuprine Hydrochloride Tablets

Category : Vasodilator.

Dose : Isoxsuprine Hydrochloride, 80 mg daily, in divided doses.

Usual strengths : 20 mg.

Standards : Isoxsuprine Tablets contain not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of Isoxsuprine Hydrochloride, $C_{18}H_{23}NO_3$. HCl.

Identification : (A) To a quantity of the powdered tablets equivalent to 50 mg of Isoxsuprine Hydrochloride add 50 ml of *0.1N hydrochloric acid* and heat on a water-bath for thirty minutes. Cool, filter, add 10 ml of *ammonia buffer pH 10.0* and extract with three quantities, each of 15 ml, of *methylene chloride.* Shake the combined extracts with 5 g of *anhydrous sodium sulphate,* filter and evaporate the filtrate to dryness. Dissolve the residue in 5 ml of *0.1N methanolic hydrochloric acid* and evaporate. Dissolve the residue in 5 ml of *methyl alcohol*, evaporate to dryness, redissolve the residue in 2 ml of *methyl alcohol,* add 15 ml of *methylene chloride,* again evaporate to dryness and dry the residue at 60° 'in vacuo' for one hour. The *infra-red absorption spectrum* of the residue exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *isoxsuprine hydrochloride R.S.* Appendix 5.15B.

(B) the light absorption, in the range 230 to 350 nm, of the solution obtained in the **Assay** exhibits maxima at 269 nm and at 274nm, Appendix 5.15A.

Other requirements : Comply with the requirements given under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 20 mg of Isoxsuprine Hydrochloride, add 50 ml of *0.1N hydrochloric acid* and boil on a water-bath for thirty minutes. Cool, dilute to 100.0 ml with *0.1N hydrochloric acid* and filter. Dilute 25.0 ml of the filtrate to 100.0 ml with *0.1N hydrochloric acid* and measure the *extinction* of the resulting solution at the maximum at about 274 nm, Appendix 5.15A. Calculate the content of $C_{18}H_{23}NO_3$, HCl from the difference between the *extinction* at 274 nm and any *extinction* at 300 nm, taking 73 as the value of E (1 per cent, 1 cm) at the maximum at about 274 nm.

Storage : Store in tightly-closed containers.

Lignocaine Hydrochloride Injection

Lingocaine Hydrochloride Injection

Category : Local anaesthetic; cardiac depressant, antiarrhythmic.

Dose : As local anaesthetic, upto 200 mg as a single dose. For treatment of cardiac arrhythmias, by intravenous injection, 50 to 100 mg at a rate of 1 to 2 mg per minute.

Usual strengths : 1.0 per cent w/v; 2.0 per cent w/v; 5.0 per cent w/v.

Standards : Lignocaine Hydrochloride Injection is a sterile solution of Lignocaine Hydrochloride in Water for Injection. It contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of $C_{14}H_{22}N_2O$, HCl, H_2O.

Identification : (A) To a volume equivalent to 0.1 g of Lignocaine Hydrochloride add sufficient *sodium hydroxide solution* to make alkaline, filter, wash the residue with *water*, dissolve it in 1 ml of *alcohol*, add 0.5 ml of a 10 per cent w/v solution of *cobalt chloride*, and shake for two minutes; a bright green colour develops and a fine precipitate is formed.

(B) To a volume equivalent to 0.1g of Lignocaine Hydrochloride add 10 ml of *trinitrophenol solution;* the melting range of the precipitate, after washing with *water* and drying at 105°, between 227°and 231°, Appendix 5.11.

(C) It gives the reactions of *chlorides*, Appendix 3.1.

pH : Between 6.0 and 7.0, Appendix 5.10.

Other requirements : Complies with the requirements stated under Injections.

Assay : Carry out the **Assay** for Lignocaine Hydrochloride described under Lignocaine and Adrenaline Injection.

Storage : Store in single-dose or multiple-dose containers.

Mercaptopurine Tablets

Category : Cytotoxic agent (anti-metabolite).

Dose : Mercaptopurine, 0.1 to 0.2 g daily, in divided doses.

Usual strengths : 50 mg.

Standards : Mercaptopurine Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of Mercaptopurine, $C_5H_4N_4S$, H_2O.

Identification : Shake a quantity of the powdered tablets equivalent to 50 mg of Mercaptopurine with a mixture of 20 ml *water* and 0.5 ml of *sodium hydroxide solution* for about 3 minutes, add sufficient *water* to produce 100 ml, mix, and filter. Dilute a suitable aliquot of the filtrate with sufficient *0.1N hydrochloric acid* to give a solution containing 5 µg of Mercaptopurine per ml. The light absorption of the resulting solution exhibits a maximum at about 325 nm, Appendix 5.15A.

Disintegration : Maximum time, thirty minutes, Appendix 5.6.1.

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powdered tablets equivalent to 50 mg of Mercaptopurine and transfer to a 100-ml volumetric flask. Add 20 ml of *water* and 1.5 ml of *N sodium hydroxide* and swirl for not more than five minutes. Dilute to volume with *water*, mix and filter, discarding the first 20 ml of the filtrate. Dilute 5.0 ml of the filtrate to 500.0 ml with *0.1N hydrochloric acid*. Determine the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 325 nm, Appendix 5.15A. Calculate the content of $C_5H_4N_4S$, H_2O taking 1165 as the value of E (1 per cent, 1 cm) at the maximum at about 325 nm.

Storage : Store in well-closed light-resistant containers.

Metformin Tablets

Metformin Hydrochloride Tablets

Category : Antidiabetic (oral).

Dose : Metformin Hydrochloride, 0.5 to 2.0 g daily, in divided doses.

Usual strengths : 0.5 g; 0.85 g.

Standards : Metformin Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Metformin Hydrochloride $C_4H_{11}N_5$, HCl. The tablets may be coated.

Identification : (A) Shake a quantity of the powdered tablets equivalent to 20 mg of metformin hydrochloride with 20 ml of *ethyl alcohol,* filter, evaporate the filtrate to dryness on a water-bath and dry the residue at 105° for one hour. The *infra-red absorption spectrum* of the dried residue exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *metformin hydrochloride R.S.* Appendix 5.15B.

(B) Triturate a quantity of the powdered tablets equivalent to 50 mg of metformin hydrochloride with 10 ml of *water* and filter; the filtrate complies with **Identification** test (B) and (D) described under metformin hydrochloride.

Dissolution : Carry out the *dissolution test for tablets and capsules,* Appendix 5.7, using 1000 ml of a 0.68 per cent w/v solution of *potassium dihydrogen phosphate* adjusted to pH 6.8 by the addition of *N sodium hydroxide,* and placing one tablet in the basket for each test. Withdraw a sample of 10 ml of the medium, filter, and measure the *extinction* of a layer of suitable thickness of the filtrate, suitably diluted if necessary, at the maximum at about 233 nm, Appendix 5.15A. Calculate the total content of metformin hydrochloride, $C_4H_{11}N_5$,HCl, taking 806 as the value of E (1 per cent, 1 cm) at the maximum at about 233 nm.

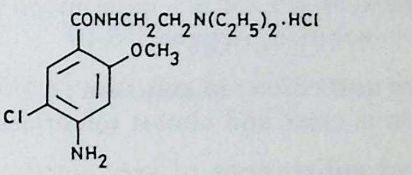
The amount of the metformin hydrochloride per tablet in the solution is not less than 70 per cent of the stated amount.

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 45 mg of metformin hydrochloride, shake for fifteen minutes with 50 ml of *water,* dilute to 100.0 ml with *water,* mix and filter. To 5.0 ml of the filtrate in a 25 ml volumetric flask add 10.0 ml of a solution prepared by dissolving 1 g of *sodium nitroprusside* and 1 g of *potassium ferrocyanide* in 50 ml of a 0.5 per cent w/v solution of *sodium hydroxide,* adding 5 ml of *hydrogen peroxide solution (30 per cent),*swirling gently, and diluting to 100 ml with the solution of sodium hydroxide. Mix, set aside for twenty minutes, dilute with *water* to volume and measure the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 525 nm, Appendix 5.15A, using as the blank a solution prepared by treating 5 ml of *water* in the same manner beginning at the words "add 10.0 ml of a solution ...". Calculate the content of $C_4H_{11}N_5$,HCl, from the *extinction* obtained by repeating the operation using 5 ml of a 0.045 per cent w/v solution of *metformin hydrochloride R.S.* and beginning at the words "add 10.0 ml of a solution..." and from the declared content of $C_4H_{11}N_5$,HCl in the *metformin hydrochloride R.S.*

Storage : Store in tightly-closed containers.

Metoclopramide Hydrochloride



$C_{14}H_{22}ClN_3O_2$. HCl,H_2O Mol. Wt. 354.27

Category : Antiemetic; accelerator of gastric emptying.

Dose : The equivalent of 10 to 30 mg of anhydrous metoclopramide hydrochloride daily, in divided doses.

By intravenous or intramuscular injection, the equivalent of 10 mg of anhydrous metoclopramide hydrochloride.

Description : White or almost white, crystalline powder; odourless or almost odourless.

Solubility : Very soluble in *water;* freely soluble in *alcohol;* sparingly soluble in *chloroform;* practically insoluble in *solvent ether.*

Standards : Metoclopramide Hydrochloride is the monohydrate of 4-amino-5-chloro-*N* (2-diethylaminoethyl)-2-methoxybenzamide hydrochloride. It contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of $C_{14}H_{22}ClN_3O_2$,HCl, calculated with reference to the anhydrous substance.

Identification : (A) The *infra-red absorption* spectrum exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *metoclopramide hydrochloride R.S.*, Appendix 5.15B.

(B) The light absorption, in the range 230 to 350 nm, of a 1-cm layer of a 0.002 per cent w/v solution in *0.01N hydrochloric acid* exhibits two maxima, at 273 nm and at 309 nm; *extinction* at 273 nm, about 0.79, and at 309 nm, about 0.69, Appendix 5.15A.

(C) Dissolve 50 mg in 5 ml of *water* and add 5 ml of a 1 per cent w/v solution of *4-dimethylaminobenzaldehyde* in *N hydrochloric acid;* a yellow-orange colour is produced.

(D) A solution (1 in 10) gives the reactions of chlorides. Appendix 3.2.2.

pH : Between 4.5 and 6.5, determined in a 10.0 per cent w/v solution, Appendix 5.10.

Clarity and colour of solution : A 10 per cent w/v solution is clear and almost colourless.

Related substances : Carry out the method for *thin-layer chromatography,* Appendix 5.4.3, using *silica gel GF 254* as the coating substance and a mixture of 95 volumes of *n-butyl alcohol* and 5 volumes of *strong ammonia solution* as the mobile phase. Apply separately to the plate 5µl of each of two solutions in *methyl alcohol* containing (1) 5.0 per cent w/v of the substance being examined and (2) 0.050 per cent w/v of the substance being examined. After removal of the plate, dry it in a current of air and examine under an ultra-violet lamp having a maximum output at about 254 nm. The spot in the chromatogram obtained with solution (2) is more intense than any spot, other than the principal spot obtained with solution (1).

Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Water : Between 4.5 per cent and 5.5 per cent w/w, determined on 0.5 g, Appendix 3.3.25.

Assay : Weigh accurately about 0.3 g into a stoppered flask, add 10 ml of *mercuric acetate solution,* 2 ml of *acetic anhydride* and allow to stand for three hours; add 80 ml of *glacial acetic acid* and titrate with *0.1N perchloric acid,* determining the end-point potentiometrically. Carry out a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.03363 g of $C_{14}H_{22}ClN_3O_2$,HCl.

Storage : Store in well-closed, light-resistant containers.

Metoclopramide Injection

Category : Antiemetic; accelerator of gastric emptying.

Dose : By intravenous or intramuscular injection, the equivalent of 10 mg of anhydrous metoclopramide hydrochloride.

Usual strength : 10 mg of anhydrous metoclopramide hydrochloride in 2 ml.

Standards : Metoclopramide Injection is a sterile solution of Metoclopramide Hydrochloride in Water for Injection, free from dissolved air. It contains suitable buffering and stabilising agents. It contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of $C_{14}H_{22}ClN_3O_2$.HCl.

Identification : (A) Dilute a volume equivalent to 10 mg of anhydrous metoclopramide hydrochloride to 500 ml with *0.01N hydrochloric acid.* The light absorption of the resulting solution, in the range 230 nm to 350 nm exhibits maxima, at 273 nm and at 309 nm, Appendix 5.15A.

(B) To a volume equivalent to 50 mg of anhydrous metoclopramide hydrochloride add 5 ml of *water* and 5 ml of a 1 per cent w/v solution of *4-dimethylamino benzaldehyde* in *N hydrochloric acid;* a yellow orange colour is produced.

pH : Between 3.0 and 5.0, Appendix 5.10.

Other requirements : Complies with the requirements stated under Injections.

Assay : Dilute a volume equivalent to 10 mg of anhydrous metoclopramide hydrochloride to 100.0 ml with *water.* To 20.0 ml add 15 ml of *1.25 N sodium hydroxide* and extract with three quantities, each of 30 ml, of *chloroform,* dry each extract with *anhydrous sodium sulphate* and filter. Dilute the combined extracts to 100.0 ml with *chloroform* and measure the *extinction* of the resulting solution at the maximum at about 305 nm, Appendix 5.15A. Calculate the content of $C_{14}H_{22}ClN_3O_2$,HCl, taking 265 as the value of E (1 per cent, 1 cm) at the maximum at about 305 nm.

Storage : Store in single-dose or multiple-dose, light-resistant containers.

Labelling : The label on the container states the strength in terms of the equivalent amount of anhydrous metoclopramide hydrochloride.

Metoclopramide Tablets

Metoclopramide Hydrochloride Tablets

Category : Antiemetic; accelerator of gastric emptying.

Dose : The equivalent of 10 to 30 mg of anhydrous metoclopramide hydrochloride daily, in divided doses.

Usual strengths : The equivalent of 10 mg of anhydrous metoclopramide hydrochloride.

Standards : Metoclopramide Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of metoclopramide hydrochloride, $C_{14}H_{22}ClN_3O_2$, HCl.

Identification : (A) Shake a quantity of the powdered tablets equivalent to 10 mg of anhydrous metoclopramide hydrochloride with 50 ml of *0.01N hydrochloric acid* and heat at 70° for fifteen minutes with frequent shaking. Cool, filter and dilute the filtrate to 200 ml with *0.01N hydrochloric acid.* The light absorption of the resulting solution, in the range 230 to 350 nm, exhibits maxima at 273 nm and at 309 nm, Appendix 5.15A.

(B) Shake a quantity of the powdered tablets equivalent to 50 mg of anhydrous metoclopramide hydrochloride with 5 ml of *water,* filter, and add to the filtrate 5 ml of a 1 per cent w/v solution of *4-dimethylaminobenzaldehyde* in *N hydrochloric acid,* a yellow-orange colour is produced.

Uniformity of content : Powder one tablet and carry out the **Assay** beginning at the words "add 50 ml of *0.1N hydrochloric acid...*". Calculate the content of *metoclopramide hydrochloride,* $C_{14}H_{22}ClN_3O_2$,HCl, in the tablet.

Repeat the operation with a further nine tablets and calculate the average content of the ten tablets. The content of each tablet is between 90 and 115 per cent of the average.

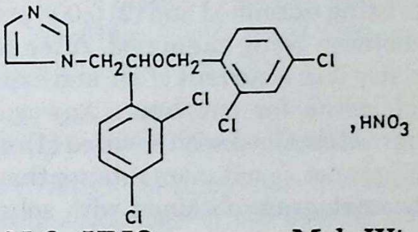
Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 10 mg of anhydrous metoclopramide hydrochloride, add 50 ml of *0.1N hydrochloric acid,* heat on a water-bath at 70° for fifteen minutes, cool, dilute to 100.0 ml with *water* and filter. Using the filtrate complete the **Assay** described under Metoclopramide Injection, beginning at the words "To 20.0 ml add...".

Storage : Store in well-closed, light-resistant containers.

Labelling : The label on the container states the strength in terms of the equivalent amount of anhydrous metoclopramide hydrochloride.

Miconazole Nitrate



$C_{18}H_{14}Cl_4N_2O$, HNO_3 Mol. Wt. 479.15

Category : Antifungal (topical).

Description: White or almost white, crystalline powder; odourless or almost odourless.

Solubility : Very slightly soluble in *water* and in *solvent ether;* slightly soluble in *alcohol* and in *chloroform.*

Standards : Miconazole Nitrate is 1-[2,4-Dichloro-β-(2,4-dichlorobenzyl) oxy phenethyl]-imidazole mononitrate. It contains not less than 98.5 per cent and not more than 101.5 per cent of equivalent to $C_{18}H_{14}Cl_4N_2O$, HNO_3, calculated with reference to the dried substance.

Identification : (A) The *infra-red absorption* spectrum exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *miconazole nitrate R.S.,* Appendix 5.15B.

(B) The light absorption, in the range 230 to 350 nm, of 1-cm layer of a 0.04 per cent w/v solution in a mixture of 9 volumes of *methyl alcohol* and 1 volume of *0.1N hydrochloric acid* exhibits three maxima, at 264 nm, 272 nm and 280 nm; *extinction* at 264 nm, about 0.40; at 272 nm, about 0.58 and at 280 nm, about 0.48, Appendix 5.15A.

(C) It melts at about 182° with decomposition, Appendix 5.11.

(D) Shake 10 mg with 5 ml of *water* and cool in an ice-bath keeping the suspension cool throughout, add 0.4 ml of a 10 per cent w/v solution of *potassium chloride,* 0.1 ml of *diphenylamine solution* and dropwise, with shaking 5 ml of *sulphuric acid;* an intense blue colour is produced.

Related substances : Carry out the method for *thin-layer chromatography,* Appendix 5.4.3, using *silica gel G* as the coating substance and a mixture of 60 volumes of *n-hexane,* 30 volumes of *chloroform,* 10 volumes of *methyl alcohol* and 1 volume of *strong ammonia solution* as the mobile phase. Apply separately to the plate 50 µl of each of two solutions in a mixture of equal volumes of *chloroform* and *methyl alcohol* containing (1) 2.0 per cent w/v of the substance being examined and (2) 0.005 per cent w/v of the substance being examined. After removal of the plate, dry it in a current of air and expose to the vapour of iodine for one hour. Any spot in the chromatogram obtained with solution (1), other than the principal spot, is not more intense than the spot in the chromatogram obtained with solution (2).

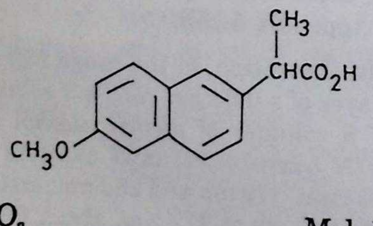
Sulphated ash : Not more than 0.2 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying 'in vacuo' at 100°, Appendix 5.8.

Assay : Weigh accurately about 0.35 g and dissolve in 50 ml of *glacial acetic acid,* warming if necessary. Cool, protecting from moisture, and titrate with *0.1N perchloric acid,* determining the end-point potentiometrically. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.04792 g of $C_{18}H_{14}Cl_4N_2O, HNO_3$.

Storage : Store in well-closed, light-resistant containers.

Naproxen



$C_{14}H_{14}O_3$ Mol. Wt. 230.26

Category : Analgesic and anti-inflammatory.

Dose : 0.25 to 1 g daily, in divided doses.

Description : White or almost white, crystalline powder; odourless or almost odourless.

Solubility : Practically insoluble in *water;* soluble in *alcohol,* in *chloroform,* and in *methyl alcohol*; sparingly soluble in *solvent ether.*

Standards : Naproxen is (+)-2-(6-methoxy-2-naphthyl)propionic acid. It contains not less than 98.5 per cent and not more than 100.5 per cent of $C_{14}H_{14}O_3$, calculated with reference to the dried substance.

Identification : (A) The *infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *naproxen R.S.,* Appendix 5.15B.

(B) The light absorption, in the range 250 to 350 nm, of a 1-cm layer of a 0.004 per cent w/v solution in *methyl alcohol* exhibits four maxima at 262 nm, 271 nm, 316 nm and 331 nm; *extinction* at 262 nm, about 0.45; at 271 nm, about 0.46; at 316 nm, about 0.13 and at 331 nm, about 0.15, Appendix 5.15A.

(C) It melts at about 156°, Appendix 5.11.

Specific optical rotation : Between + 63° and +68.5°, determined on a 4 per cent w/v solution in *chloroform,* Appendix 5.12.

Related substances : Carry out the method for *thin-layer chromatography,* Appendix 5.4.3, using *silica gel GF 254* as the coating substance and a mixture of 180 volumes of *toluene,* 18 volumes of *tetrahydrofuran* and 6 volumes of *glacial acetic acid* as the mobile phase. Apply separately to the plate 10 µl of each of two solutions in *methyl alcohol* containing (1) 2.0 per cent w/v of the substance being examined and (2) 0.01 per cent w/v of the substance being examined. After removal of the plate, dry it in a current of air and examine under an ultra-violet lamp having a maximum output at about 254 nm. The spot in the chromatogram obtained with solution (2) is more intense than any spot in the chromatogram other than the principal spot, obtained with solution (1).

Residual organic bases : Dissolve 3.5 g in 100 ml of *dichloromethane* and extract with three quantities, each of 10 ml, of *0.1N hydrochloric acid.* Wash the combined aqueous extracts with two quantities, each of 10 ml, of *dichloromethane.* To

20 ml of the aqueous layer add 5 ml of a 30 per cent w/v solution of *sodium chloride,* 15 ml of *n-butyl alcohol* and 1 ml of a 5 per cent w/v of *cuprous chloride.* Shake for thirty seconds, add 3 ml of *6N sodium hydroxide,* shake for a further thirty seconds and centrifuge. To 10 ml of the butyl alcohol layer add 3 ml of *methyl alcohol* and mix. Measure the *extinction* of the resulting solution at the maximum at about 274 nm, Appendix 5.15A, using as the blank a solution prepared in the same manner but omitting the substance being examined. The *extinction* is not greater than 0.20.

Heavy metals : Not more than 20 parts per million, determined on 1.0 g by method B, Appendix 3.2.4.

Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7. Use 1.5 g and ignite at a temperature of about 600°.

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105° for three hours, Appendix 5.8.

Assay : Weigh accurately about 0.5 g and dissolve in a mixture of 75 ml of *methyl alcohol and 25ml of water.* Titrate with carbonate-free *0.1N sodium hydroxide* using *phenolphthalein solution* as indicator. Each ml of *0.1N sodium hydroxide* is equivalent to 0.02303 g of $C_{14}H_{14}O_3$.

Storage : Store in tightly-closed, light resistant containers.

Naproxen Tablets

Category : Analgesic and anti-inflammatory.

Dose : Naproxen, 0.25 g to 1 g daily, in divided doses.

Usual strengths : 0.25 g; 0.5 g.

Standards : Naproxen Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of $C_{14}H_{14}O_3$.

Identification : (A) Extract a quantity of the powdered tablets equivalent to 20 mg of Naproxen with sufficient *methyl alochol* to produce 100 ml and filter. Reserve 10 ml of the filtrate for **Identification** test (B), evaporate the remainder and dry the residue at 105°. The *infra-red absorption spectrum* of the dried residue exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *naproxen R.S.,* Appendix 5.15B.

(B) Dilute the 10 ml portion of the filtrate reserved in **Identification** test (A) to 100 ml with *methyl alcohol.* The *extinction* of the resulting solution exhibits maxima at 262 nm, at 271 nm, at 316 nm and at 331 nm, Appendix 5.15A.

(C) Extract a quantity of the powdered tablets equivalent to 10 mg of Naproxen with **chloroform,** filter and evaporate the filtrate to dryness. The residue, after crystallisation from *chloroform* and drying at 105°, melts at about 156°, Appendix 5.11.

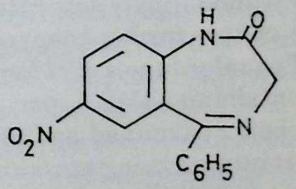
Related substances : Comply with the test described under Naproxen, using as solution (1) a solution prepared by extracting a quantity of the powdered tablets equivalent to 0.5 g of Naproxen with 25 ml of *methyl alcohol* and filtering; for solution (2) dilute 1 volume of solution (1) to 200 volumes with *methyl alcohol.*

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to about 0.05 g of Naproxen, shake with 70 ml of *methyl alcohol* for thirty minutes, add sufficient *methyl alcohol* to produce 100.0 ml and filter. Dilute 5.0 ml of the filtrate to 50.0 ml with *methyl alcohol* and measure the *extinction* of the resulting solution at the maximum at about 331 nm, Appendix 5.15A. Calculate the content of $C_{14}H_{14}O_3$, taking 81 as the value of E (1 per cent, 1 cm) at the maximum at about 331 nm.

Storage : Store in light-resistant containers.

Nitrazepam



$C_{15}H_{11}N_3O_3$ Mol. Wt. 281.26

Category : Hypnotic and Sedative.

Dose : 5 to 10 mg daily.

Description : Yellow, crystalline powder; odourless or almost odourless.

Solubility : Practically insoluble in *water;* slightly soluble in *alcohol* and in *solvent ether;* sparingly soluble in *chloroform.*

Standards : Nitrazepam is 1,3-dihydro-7-nitro-5-phenyl-2*H*-1, 4-benzodiazepin-2-one. It contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of $C_{15}H_{11}N_3O_3$, calculated with reference to the dried substance.

Identification : (A) The light absorption, in the range 230 to 350 nm, of a 1-cm layer of a freshly prepared 0.0005 per cent w/v solution in a 0.5 per cent w/v solution of *sulphuric acid* in *methyl alcohol* exhibits a maximum only at 280 nm, *extinction* at 280 nm, about 0.45, Appendix 5.15A.

(B) Dissolve 10 mg in 1 ml of *methyl alcohol,* warming if necessary, and add 0.05 ml of *2N sodium hydroxide;* an intense yellow colour is produced.

(C) Dissolve 20 mg in a mixture of 5 ml of *hydrochloric acid* and 10 ml of *water,* boil for five minutes, cool, and add 2 ml of a 0.1 per cent w/v of *sodium nitrite.* Allow to stand for one minute, add 1 ml of a 0.5 per cent w/v solution of *sulphamic acid,* mix, allow to stand for one minute and add 1 ml of a 0.1 per cent w/v solution of *N-(1-napthyl)-ethylenediamine hydrochloride;* a red colour is produced.

(D) It melts at about 226° with decomposition, Appendix 5.11.

Related substances and decomposition products : Carry out in subdued light the method for *thin-layer chromatography,* Appendix 5.4.3, using *silica gel GF 254* as the coating substance and a mixture of 85 volumes of *nitromethane* and 15 volumes of *ethyl acetate* as the mobile phase, but allowing the solvent front to ascend 12 cm above the line of application. Apply separately to the plate 10 µl of each of two freshly-prepared solutions in a mixture of equal volumes of *chloroform* and *methyl alcohol* containing (1) 2.5 per cent w/v of the substance being examined and (2) 0.0025 per cent w/v of the substance being examined. After removal of the plate, allow the solvent to evaporate and examine under an ultra-violet lamp having a maximum output at about 254 nm. The spot in the chromatogram obtained with solution (2) is more intense than any spot, other than the principal spot, in the chromatogram obtained with solution (1).

Heavy metals : Not more than 20 parts per million, determined on 1.0 g by method B, Appendix 3.2.4.

Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g by drying in an oven at 105° for four hours, Appendix 5.8.

Assay : Weigh accurately about 0.5 g, dissolve in 50 ml of *acetic anhydride* and titrate with *0.1N perchloric acid* using 0.25 ml of *nile blue A solution* as indicator until a yellowish-green colour is obtained. Carry out a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.02813 g of $C_{15}H_{11}N_3O_3$.

Storage : Store in tightly-closed, light-resistant containers.

Nitrazepam Tablets

Category : Hypnotic and sedative.

Dose : Nitrazepam, 5 to 10 mg daily.

Usual strengths : 5 mg; 10 mg.

Standards : Nitrazepam tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of nitrazepam, $C_{15}H_{11}N_3O_3$.

Identification : (A) The light absorption, in the range 230 to 350 nm, of the final solution obtained in the **Assay** exhibits a maximum only at 280 nm, Appendix 5.15A.

(B) Carry out the method for *thin-layer chromatography,* Appendix 5.4.3, using *silica gel G* as the coating substance and a mixture of 10 volumes of *chloroform* and 1 volume of *methyl alcohol* as the mobile phase. Apply separately to the plate 2µl of each of the following solutions. For solution (1) shake a quantity of the powdered tablets with sufficient *methyl alcohol* to produce a solution containing 5 mg of Nitrazepam per ml, allow to settle and decant the supernatant liquid; solution (2) is a 0.5 per cent w/v of *nitrazepam R.S.* in *methyl alcohol.* After removal of the plate, spray it with a 10 per cent v/v solution of *sulphuric acid* in *ethyl alcohol,* heat at 105° for 10 minutes and examine under an ultra-violet lamp having a maximum output at about 360 nm. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

(C) To a quantity of the powdered tablets equivalent to 5 mg of Nitrazepam add 5 ml of *hydrochloric acid* and 10 ml of *water,* heat on a water-bath for fifteen minutes and filter. To the clear filtrate add 1 ml of 0.1 per cent w/v solution of *sodium nitrite,* allow to stand for three minutes, and add 1 ml of a 0.5 per cent w/v solution of *sulphamic acid.* Allow to stand for three minutes and add 1 ml of 0.1 per cent w/v solution of *N-(1-naphthyl)ethylenediamine hydrochloride;* a red colour is produced.

Related substances and decomposition products : Comply with the test described under Nitrazepam, using a mixture of 40 volumes of *nitromethane,* 40 volumes of *toluene* and 20 volumes of *chloroform* as the mobile phase and applying separately to the plate 5 µl of the following two freshly prepared solutions. For solution (1) shake a quantity of the powdered tablets equivalent to 40 mg of Nitrazepam with 25 ml of *chloroform,* filter, carefully evaporate the filtrate to dryness and dissolve the residue in 2 ml of *chloroform;* for solution (2) dilute 1 volume of solution (1) to 200 volumes with *chloroform.*

Uniformity of content : Powder one tablet, add 5 ml of *water,* mix and allow to stand for fifteen minutes. Add 90 ml of a 0.5 per cent v/v solution of *hydrochloric acid* in *methyl alcohol,* shake for fifteen minutes, add sufficient volume of the *hydrochloric acid solution* to produce 100.0 ml and filter. Dilute 10.0 ml of the filtrate with a sufficient volume of the acid solution to produce a solution containing 0.0005 per cent w/v of Nitrazepam. Measure the *extinction* of the resulting solution at the maximum at about 280 nm, Appendix 5.15A. Calculate the content of $C_{15}H_{11}N_3O_3$, taking 910 as the value of E(1 per cent, 1 cm) at the maximum at about 280 nm.

Repeat the operation with a further nine tablets and calculate the average content of the ten tablets. The content of each tablet is between 90 and 110 per cent of the average, except that for one tablet the content may be between 85 and 115 per cent of the average.

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 5 mg of Nitrazepam, add 5 ml of *water,* mix, and allow to stand for fifteen minutes. Add 90 ml of a 0.5 per cent w/v solution of *hydrochloric acid* in *methyl alcohol,* shake for fifteen minutes, add sufficient of the hydrochloric acid solution to produce 100.0 ml and filter. Dilute 10.0 ml of the filtrate to 100.0 ml with the same solution and measure the *extinction* of the resulting solution at the maximum at about 280 nm, Appendix 5.15A. Calculate the content of $C_{15}H_{11}N_3O_3$, taking 910 as the value of E (1 per cent, 1 cm) at the maximum at about 280 nm.

Storage : Store in well-closed, light-resistant containers.

पुस्तकालय

Diluted Pentaerythritol Tetranitrate

$C_5H_8N_4O_{12}$ Mol. Wt. 316.14

Category : Vasodilator, antianginal.

Dose : 20 to 60 mg of pentaerythritol tetranitrate, three to four times daily.

Description : White or almost white, powder; odour, faint and mild.

Standards : Diluted Pentaerythritol Tetranitrate is a dry mixture of 2, 2-bis(hydroxymethyl)-1,3-propanediol tetranitrate with Lactose or Mannitol or a mixture of Lactose and Starch or any other suitable inert excipients which permit safe handling. It contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of $C_5H_8N_4O_{12}$.

Identification : (A) Transfer a quantity equivalent to 10 mg of pentaerythritol tetranitrate to a medium porosity sintered-glass filter, add 5 ml of *acetone* and collect the filtrate. Repeat with two further quantities, each of 5 ml, of *acetone* and evaporate the combined filtrate at a temperature not exceeding 60° for four hours; the dried residue melts between 138° and 142°, Appendix 5.11.

(B) Suspend 10 mg of the residue obtained in **Identification** test (A) in a mixture of 2 ml of *sulphuric acid* and 1 ml of *water;* cool and carefully overlay with 3 ml of *ferrous sulphate solution;* a reddish brown colour is produced at the interface of the two liquids.

Heavy metals : Not more than 10 parts per million, determined on 2.0 g by method B, Appendix 3.2.4.

Assay : Weigh accurately a quantity equivalent to about 50 mg of pentaerythritol tetranitrate and transfer to a 100-ml volumetric flask with the aid of about 30 ml of *acetone.* Add sufficient *acetone* to produce 50 ml and warm on a water-bath at a temperature not exceeding 60° and boil gently, with occasional swirling, for five minutes. Cool, dilute to volume with *acetone* and mix. Transfer a portion of the mixture to a glass-stoppered centrifuge tube and centrifuge at 1500 rpm for five minutes. Transfer 1.0 ml of the supernatant solution to a 100-ml volumetric flask and evaporate at 35° with the aid of a current of air to dryness. To the residue add 1.0 ml of *glacial acetic acid* and swirl to disolve. Add 2 ml of *phenoldisulphonic acid solution,* mix and allow to stand for five minutes. Add 25 ml of *water* and 10 ml of *strong ammonia solution,* cool, dilute to volume with *water* and mix. Measure the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 409 nm, Appendix 5.15A, using *water* as the blank.

Weigh accurately 0.130 g of *potassium nitrate,* previously dried at 105° for four hours, and dissolve in 3 ml of *water* , dilute with sufficient *glacial acetic acid* to produce 200.0 ml and mix well. Using 1.0 ml of the this solution repeat the **Assay** beginning at the words "add 2 ml of *phenoldisulphonic acid solution* ...". Calculate the content of $C_5H_8N_4O_{12}$ from the values of the *extinctions* so obtained. Each ml of the potassium nitrate solution is equivalent to 0.503 mg of $C_5H_8N_4O_{12}$.

Storage : Store in tightly-closed, light-resistant containers, in a cool place.

Pentaerythritol Tetranitrate Tablets

Category : Vasodilator, antianginal.

Dose : Pentaerythritol Tetranitrate, 10 to 30 mg, three to four times daily.

Usual strengths : 10 mg; 30 mg.

Standards : Pentaerythritol Tetranitrate Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of pentaerythritol tetranitrate, $C_5H_8N_4O_{12}$

Identification : The powdered tablets comply with the **Identification** test given under Diluted Pentaerythritol Tetranitrate.

Other requirements : Comply with the requirements stated under Tablets.

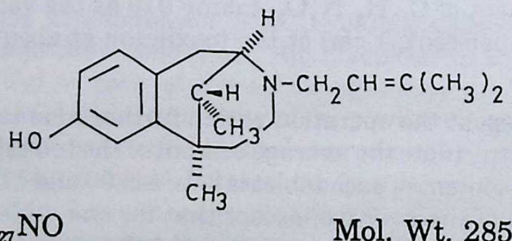
Uniformity of content (for 10 mg tablets only) : Crush one tablet and transfer to a 50-ml volumetric flask with the aid of 15 ml of *acetone.* Add sufficient *acetone* to produce 25 ml, heat the mixture on a water-bath at a temperature not exceeding 60° and boil gently, with occasional swirling, for five minutes. Cool, dilute to volume with *acetone* and mix. Transfer a portion of the mixture to a glass-stoppered centrifuge tube and centrifuge at 1500 rpm for five minutes. Transfer 2.5 ml of the supernatant solution to a 100-ml volumetric flask and evaporate at 35° with the aid of a current of air to dryness. Complete the **Assay** described under Diluted Pentaerythritol Tetranitrate, beginning at the words. "To the residue add 1.0 ml of *glacial acetic acid* ...". Calculate the content of $C_5H_8N_4O_{12}$ in the tablet.

Repeat the operation using further nine tablets. The content of each tablet is between 85 and 115 per cent of the average except that for one tablet the content may be between 80 and 120 per cent of the average.

Assay : Weigh and powder 20 tablets. With suitable quantity of the powder carry out the **Assay** described under Diluted Pentaerythritol Tetranitrate.

Storage : Store in tightly-closed, light-resistant containers in a cool place.

Pentazocine



$C_{19}H_{27}NO$ Mol. Wt. 285.43

Category : Analgesic

Dose : By intramuscular, intravenous, or subcutaneous injection 30 to 60 mg.

Description : White or creamy-white powder; almost odourless.

Solubility : Practically insoluble in *water;* freely soluble in *chloroform;* soluble in *alcohol,*in *acetone,* and in *solvent ether;* sparingly soluble in *benzene* and in *ethyl acetate.*

Standards : Pentazocine is (2*R*,6*R*,11*R*)-1,2,3,4,5,6-hexahydro-6-11-dimethyl-3-(3-methylbut-2-enyl)-2,6-methano-3-benzazocin-8-ol. It contains not less than 98.0 per cent and not more than 101.0 per cent of $C_{19}H_{27}NO$, calculated with reference to the dried substance.

Identification : (A) The *infra-red absorption spectrum* exhibits maxima which are only at the same wavelength as, and have similar relative intensities to, those in the spectrum of *pentazocine R.S.,* Appendix 5.15B.

(B) To 1 mg in a porcelain crucible, add 0.5 ml of a solution of *sulphuric acid* containing 1 per cent w/v of *ammonium molybdate;* an intense blue colour is produced which changes to bluish-green, green, and finally, on standing, to yellow.

(C) Dissolve 5 mg in 5 ml of *sulphuric acid,* add one drop of a 9 per cent w/v solution of *ferric chloride* and mix; a yellow colour is produced which becomes deeper slightly on warming. On the addition of a drop of *nitric acid* the colour is unchanged.

Melting range : Between 150° and 155°, with slight darkening, Appendix 5.11.

Light absorption : To 0.10 g add 20 ml of *water* and 1 ml of *N hydrochloric acid,* shake to dissolve, and add sufficient *water* to produce 100.0 ml. Dilute 10.0 ml to 100.0 ml with *water* containing 1 ml of *N hydrochloric acid.* Extinction of a 1-cm layer of the resulting solution at the maximum at about 278 nm, 0.67 to 0.71, Appendix 5.15A.

Related substances : Carry out the method for *thin-layer chromatography,* Appendix 5.4.3., using *silica gel HF 254* as the coating substance and a mixture of 94 volumes of *chloroform,* 3 volumes of *methyl alcohol* and 3 volumes of *isopropylamine* as the mobile phase. Apply separately to the plate 10 µl of each of the two solutions in *chloroform* containing (1) 2.0 per cent w/v of the substance being examined and (2) 0.02 per cent w/v of *pentazocine R.S.* After removal of the plate, heat at 105° for fifteen minutes, allow to cool, and expose to the vapour of *iodone.* Any spot in the chromatogram obtained with solution (1), other than the principal spot, is not more intense than the spot in the chromatogram obtained with solution (2) and not more than two additional spots are present.

Sulphated ash : Not more than 0.2 per cent, Appendix 3.2.7.

Loss on drying : Not more than 1.0 per cent, determined in 1.0 g by drying 'in vacuo' at 60° for four hours, Appendix 5.8.

Assay : Weigh accurately about 6.0 g, dissolve in 50 ml of *glacial acetic acid,* add one drop of *crystal violet solution* and titrate with *0.1N perchloric acid* to a green end-point. Perform a blank determination and make necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.02854 g of $C_{19}H_{27}NO$.

Storage : Store in tightly-closed, light-resistant containers.

Pentazocine Injection

Pentazocine Lactate Injection

Category : Analgesic.

Dose : By subcutaneous or intramuscular injection, the equivalent of 30 to 60 mg of pentazocine every three to four hours. By intravenous injection, the equivalent of 30 mg of pentazocine, every three to four hours.

Usual strength : The equivalent of 30 mg of pentazocine in 1 ml; 60 mg of pentazocine in 2 ml.

Standards : Pentazocine Injection is a sterile solution in Water for Injection of pentazocine lactate prepared from Pentazocine with the aid of Lactic acid. It contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of pentazocine, $C_{19}H_{27}NO$.

Description : Colourless or almost colourless solution; odour, faint and characteristic of lactic acid.

Identification : (A) To a volume equivalent to 90 mg of pentazocine add 5 ml of *0.1N sodium hydroxide,* and shake the resulting solution with 5 ml of *chloroform.* Wash the *chloroform* extract with 2 ml of *water,* dry over *anhydrous sodium sulphate* and filter. Evaporate the solvent without applying heat and dry the oily residue 'in vacuo' for one hour at a temperature not exceeding 25°. The *infra-red absorption spectrum* of the residue exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to those in the spectrum of *pentazocine R.S.*, Appendix 5.15B.

(B) To a volume equivalent to 30 mg of pentazocine add 2 ml of *0.1N sodium hydroxide,* extract with 2 ml of *chloroform* and evaporate 0.1 ml of the chloroform extract to dryness in a crucible; add to the residue 0.3 ml of a solution of *sulphuric acid* containing 1 per cent w/v of *ammonium molybdate;* an intense blue colour is produced which changes to blue-green, green and on standing, to yellow.

(C) To a volume equivalent to 60 mg of pentazocine add 2 ml of *water,* make alkaline with *sodium carbonate solution* and shake with two quantities, each of 10 ml, of *chloroform.* Acidify the aqueous solution with *N sulphuric acid* and add a little *potassium permanganate.* On warming, the odour of acetaldehyde is produced.

pH : Between 4.0 and 5.0, Appendix 5.10.

Related substances : Complies with the test described under Pentazocine, using the following solutions. For solution (1) dilute a volume of the injection with *alcohol* to contain the equivalent of 2.0 per cent w/v of pentazocine. Solution (2) is a 0.02 per cent w/v solution of *Pentazocine R.S.* in *Chloroform.*

Other requirements : Complies with the requirements stated under Injections.

Assay : To a volume equivalent to 150 mg of pentazocine add sufficient *water* to produce 100.0 ml. To 5.0 ml add 1 ml of *N hydrochloric acid,* dilute to 100.0 ml with *water,* and measure the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 278 nm, Appendix 5.15A. Calculate the content of $C_{19}H_{27}NO$ taking 69 as the value of E (1 per cent, 1 cm) at the maximum at about 278 nm.

Storage : Store in single-dose, light-resistant containers.

Labelling : The label on the container states the strength in terms of the equivalent amount of pentazocine in a suitable dose-volume.

Pentazocine Tablets

Pentazocine Hydrochloride Tablets

Category : Analgesic

Dose : Pentazocine Hydrochloride, 25 to 100 mg after food.

Usual strengths : 25 mg.

Standards : Pentazocine Tablets contain not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of Pentazocine Hydrochloride, $C_{19}H_{27}NO$, HCl. The tablets may be coated.

Identification : (A) Shake a quantity of the powdered tablets equivalent to 100 mg of Pentazocine Hydrochloride with 5 ml of *ethyl alcohol* and centrifuge. Evaporate the alcohol without applying heat and dry the oily residue overnight 'in vacuo' at a temperature not exceeding 25°. The *infra-red absorption spectrum* of the residue exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *pentazocine hydrochloride R.S.*, Appendix 5.15B.

(B) Shake a quantity of the powdered tablets equivalent to 50 mg of Pentazocine Hydrochloride with 3 ml of *0.1N sodium hydroxide* and 3 ml of *chloroform,* and allow to separate. Evaporate 0.1 ml of the chloroform extract to dryness in a crucible; add to the residue 0.5 ml of a solution of *sulphuric acid* containing 1 per cent w/v of *ammonium molybdate;* an intense blue colour is produced which changes to blue-green, green and on standing, to yellow.

(C) Shake a quantity of the powdered tablets equivalent to 25 mg of Pentazocine Hydrochloride with 5 ml of *water* and 1 ml of *N nitric acid* for one minute, and filter. The filtrate gives the reactions of *chlorides,* Appendix 3.1.

Related substances : Comply with the test described under Pentazocine Hydrochloride, using the following solutions. For solution (1) add to a quantity of the powdered tablets equivalent to 0.1 g of Pentazocine Hydrochloride 5 ml of *0.1N sodium hydroxide* and 5 ml of *chloroform,* shake, allow to separate, and use the chloroform layer; solution (2) is a 0.02 per cent w/v solution of *Pentazocine Hydrochloride R.S.* in *chloroform.*

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 25 mg of Pentazocine Hydrochloride, shake with 100 ml of *water* for fifteen minutes, add 2.5 ml of

N hydrochloric acid and sufficient *water* to produce 250.0 ml and filter. Measure the *extinction* of a 1-cm layer of the filrate at the maximum at about 278 nm, Appendix 5.15A. Calculate the content of $C_{19}H_{27}NO,HCl$, taking 61 as the value of E (1 per cent, 1 cm) at the maximum at about 278 nm.

Storage : Store in tightly-closed, light-resistant containers.

Poliomyelitis Vaccine (Oral)

Poliomyelitis Vaccine (Live, Poliovirus Vaccine Oral)

Category : Active Immunising agent.

Dose : Three doses of tri-valent vaccine six to eight weeks apart and a booster eight to twelve months later, each dose consisting of 0.1 ml or 2 drops containing the specified virus concentration of the three Polio Virus types.

Description : Clear liquid which may have a reddish colour if phenol red has been used in its preparation.

Standards : Poliomyelities Vaccine (Oral) is an aqueous suspension of three types 1, 2, & 3 of live attenuated poliovirus strains (Sabin) of known history and originally obtained from WHO Monovalent Polio Vaccine bulk of each type are tested for neurovirulence in monkeys in comparison with respective Standard Neurovirulence Reference Poliovirus.

The final vaccine represents not more than three sub-cultures of types 1 & 2 and not more than two sub-cultures of type 3 from the vaccine on which tests for suitability were done. For type 3 polio vaccine the working seed can also be S.O.R. +1. The virus of each type is grown with aseptic precautions, in cultures of suitable tissue, free from extraneous micro-organisms, and adventitious agents. The medium for maintaining cell growth, as distinct from that for initiating it, contains no serum but may contain a suitable pH indicator such as phenol red. Suitable antibiotic in small concentrations may be used but penicillin and streptomycin may not be used. The medium is maintained at a temperature not exceeding 35°C during the growth of the virus.

The harvesting of virus is done within four days of inocculation and the virus suspension is tested for identity, sterility and freedom from adventitious viral agents. Harvests which pass these tests are pooled and filtered through a bacteria proof filter.

NOTE— The manufacturing method or process or the conditions under which it is conducted as given in the above standards may be modified provided the manufacturer presents to the Licensing Authority under the Drugs & Cosmetics Rule, 1945 evidence to show that the modification will provide assurance of the safety, purity and potency of the vaccine that are equal to or greater than the assurance provided by these standards. The filtered virus harvest is tested for identity and virus concentration. The polio virus in the filtered bulk suspension is also tested in comparison with appropriate reference virus preparation for (a) neurovirulence in suitable species of monkeys by intra-spinal inocculation and statistical evaluation of the severity of local reaction and the degree of its spread in the CNS, (b) the reproductive capacity at supraoptimal temperature of 40°C, $(RTC)_{40}$ by growing the virus for types 1 and 2 at 36° and 40° for type 3 at 36° C and 40.3° C and to show that the vaccine virus strain does not multiply at elevated temperatures. The final vaccine is constituted by combining appropriate dilutions of the three virus types and by the addition of approved additives.

Identification : When neutralised with appropriate specific poliomyelitis antiserum, it is unable to infect susceptible tissue cultures.

Freedom from adventitious viral agents : When neutralised with type-specific poliomyelitis antiserum or antisera, the neutralised mixture, when inocculated into susceptible tissue cultures does not show the presence of adventitious viral agents.

Sterility : Complies with the test for sterility, Appendix 4.6

Undue Toxicity : Complies with the test for undue toxicity for vaccines and sera, Appendix 2.3.7.

NOTE : Care should be taken in case of preparations that may be innocuous when taken orally but that could cause damage when injected parenterally because of a high salt content or other component. Under such conditions the test may be performed with a suitable dilution of the vaccine.

Virus concentration : Titrate for live virus by macro or micromethods using 0.5 log 10 dilutions.

The estimated mean virus titre should not be less than the declared titre, for type 1 the titre should be 10^6 $TCID_{50}$, and for type 2 the titre should be 10^5 $TCID_{50}$ and for type 3 the titre should be $10^{5.5}$ $TCID_{50}$ per single human dose. The fiducial limits of the assay ($p=0.95$) should not differ by more than $\pm 10^{0.5}$ from the estimated number of infectious units in the vaccine.

pH : Between 6.5 and 7.0 and should be stable on storage, Appendix 5.10.

Stability : Incubate the representative final containers of the trivalent vaccine at 37°C for 48 hours. Determine in parallel with a trivalent reference preparation the total virus content in exposed and control (unexposed) vials. The vaccine passes the test when the loss after exposure is not greater than 0.5 log 10 and where the post exposure is not less than $10^{5.65}$ $TCID_{50}$ or p.f.u. per dose after correction from the reference preparation.

Storage : Store in single dose or multiple dose containers in the frozen state at –20°C or below. When thawed it should be kept at a temperature of 2°C to 8°C and used within four months. If stored at a temperature between 15°C and 20°C it should be used within a few hours.

Labelling : The label on the container states (1) the type or types of poliomyelitis virus, (2) the concentration of different polio viruses, (3) the recommended dose (in drops and in ml) and number of doses in the container, (4) that the vaccine is for oral administration only, (5) the name(s) and proportion of any added preservatives or stabilizer, (6) the name(s) and amount of any antibiotics used in the preparation, (7) the storage conditions, (8) dates of manufacture and expiry, (9) name of the manufacturer and licence number.

Promethazine Injection

Promethazine Hydrochloride Injection

Category : Antihistaminic, anti-emetic, sedative

Dose : Promethazine Hydrochloride, by intramuscular injection, 25 to 50 mg daily.

Usual strengths : 25 mg in 1 ml; 50 mg in 2 ml.

Standards : Promethazine Injection is a sterile solution of Promethazine Hydrochloride in Water for Injection, free from dissolved air; it contains suitable stabilising agents. It contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of $C_{17}H_{20}N_2S, HCl$.

Identification : (A) Complies with **Indentification test** (B) described under Promethazine Hydrochloride, applying to the plate 2µl of each of the following solutions. For solution (1), add 20 ml of *water* and 2 ml of *10N sodium hydroxide* to a volume equivalent to 0.1 g of Promethazine Hydrochloride, shake and extract the mixture with 25 ml of *solvent ether*. Wash the solvent ether extract with two quantities, each of 5 ml, of *water,* dry with *anhydrous sodium sulphate* and evaporate the solvent . Add 0.1 ml of *N hydrochloric acid* to the residue and dissolve in 50 ml of *chloroform*. Solution (2) is a 0.2 per cent w/v of *promethazine hydrochloride R.S.* in *chloroform*.

(B) To a volume equivalent to 5 mg of Promethazine Hydrochloride add carefully 2 ml of *sulphuric acid* and allow to stand for five minutes; a red colour is produced.

(C) To a volume equivalent to 0.2 g of Promethazine Hydrochloride add sufficient *potassium carbonate* to saturate the solution, extract with two quantities, each of 10 ml, of *solvent ether* and evaporate the combined extracts to dryness. Dissolve the residue in 2 ml of *methyl alcohol* and pour into a solution of 0.4 g of *trinitrophenol* in 10 ml of *methyl alcohol,* previously warmed to about 50°. Cool, scratch the tube to induce crystallisation allow to stand for three to four hours, and filter. The residue, after washing with *methyl alcohol* melts at about 160°, Appendix 5.11.

pH : Between 5.0 and 6.0, Appendix 5.10.

Related impurities : Complies with the test described under Promethazine Hydrochloride, using for solution (1) a volume of the Injection diluted, if necessary, with *methyl alcohol* to contain the equivalent of 2.0 per cent w/v of Promethazine Hydrochloride.

Other requirements : Complies with the requirements stated under Injections.

Assay : Protect the solution from light throughout the assay.

To a volume equivalent to 25 mg of Promethazine Hydrochloride add sufficient *0.01N hydrochloric acid* to produce 100.0 ml. Dilute 10.0 ml to 100.0 ml with *0.01N hydrochloric acid;* then dilute 10.0 ml of this solution to 50.0 ml with *0.01N hydrochloric acid;* measure the *extinction* of the resulting solution at the maximum at about 249 nm, Appendix 5.15A. Calculate the content of $C_{17}H_{20}N_2S$, HCl, taking 910 as the value of E (1 per cent, 1 cm) at the maximum at about 249 nm.

Storage : Store in light-resistant containers.

Propantheline Tablets

Propantheline Bromide Tablets

Category : Anticholinergic.

Dose : Propantheline Bromide, upto 45 mg daily, in divided doses.

Usual strength : 15 mg.

Standards : Propantheline Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Propantheline Bromide, $C_{23}H_{30}BrNO_3$. The tablets are sugar-coated.

Identification : Triturate a quantity of the powdered tablets equivalent to 75 mg of Propantheline Bromide with 10 ml of *chloroform,* filter, remove the chloroform, by evaporation on a water-bath and stir the residue with 5 ml of *solvent ether* until a solid is obtained. The solid complies with the following tests.

(A) Dissolve 60 mg in 2 ml of *water*, add 2 ml of *sodium hydroxide solution,* boil for two minutes, cool, acidify with *2N hydrochloric acid,* heat to boiling, add *alcohol* dropwise until the precipitate just dissolves, and cool. The precipitate, after washing with *water*, recrystallisation from *alcohol (50 per cent)* and drying at 105° for one hour, melts at about 215°, Appendix 5.11. The precipitate dissolves in *sulphuric acid* to give a bright yellow solution which fluoresces in ultra-violet light.

(B) It gives the reactions of *bromidies,* Appendix 3.1.

Xanthanoic acid : Transfer the combined ether extracts obtained in the **Assay** to a separating funnel and extract with two quantities, each of 30 ml, of *0.1N sodium hydroxide* containing 1.5 per cent w/v of *sodium chloride.* Heat the combined aqueous extracts on a water-bath until the odour of ether is not perceptible, add sufficient *0.1N sodium hydroxide* to produce 100.0 ml; mix well and dilute 25.0 ml to 100.0 ml with *0. 1N sodium hydroxide. Extinction* of a 1-cm layer of the resulting solution at the maximum at about 248 nm, not more than 0.31, Appendix 5.15A.

Other requirements : Complies with the requirements stated under Tablets.

Assay : Weigh and powder 40 tablets. Weigh accurately a quantity of the powdered tablets equivalent to 0.5 g of Propantheline Bromide and transfer to a sintered glass filter. Add 10 ml of freshly distilled *peroxide-free solvent ether,* stir, and filter. Repeat the extraction with four quantities, each of 10 ml, of the *ether* and reserve the combined ether extracts for the test for **Xanthanoic acid.** Extract the residue on the filter with four quantities, each of 10 ml, of *chloroform,* evaporate the combined extracts on water bath to about 10 ml. Add 20 ml of *anhydrous glacial acetic acid,* 15 ml of *mercuric acetate solution,* a few drops of *crystal violet solution* and titrate with *0.1N perchloric acid* to a blue-green end-point. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.04484 g of $C_{23}H_{30}BrNO_3$.

Storage : Store in tightly-closed containers.

Propranolol Injection

Propranolol Hydrochloride Injection

Category : Cardiac depressant, antiarrhythmic (beta-adrenergic blocking agent).

Dose : Propranolol Hydrochloride. By slow intravenous injection, upto 1 mg.

Usual strength : 1 mg in 1 ml.

Standards : Propranolol Injection is a sterile solution of Propranolol Hydrochloride in Water for injection. The solution may contain Citric Acid. It contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of $C_{16}H_{21}NO_2$, HCl.

Identification : The light absorption of the solution obtained in the **Assay** exhibits maxima at 290 nm, 306 nm and 319 nm, Appendix 5.15A.

pH : Between 2.8 and 3.5, Appendix 5.10.

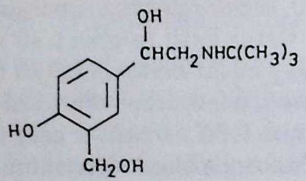
Other requirements : Complies with requirements stated under injections.

Assay : To a volume equivalent to 2 mg of Propranolol Hydrochloride add sufficient *methyl alcohol* to produce 100.0 ml. Measure the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 290 nm, Appendix 5.15A. Calculate the content of $C_{16}H_{21}NO_2$, HCl, taking 210 as the value of E (1 per cent, 1 cm) at the maximum at about 290 nm.

Storage : Store in single-dose, light-resistant containers.

Salbutamol

Albuterol



$C_{13}H_{21}NO_3$ Mol.Wt. 239.30

Category : Bronchodilator (beta-adrenoceptor stimulant).

Dose : For chronic bronchial asthma or as prophylactic, 2 inhalations of 100 µg 3 or 4 time daily, as an aerosol.

For the relief of acute bronchospasm, 1 or 2 inhalations of 100 µg as a single dose when required.

Description : White or almost white, crystalline powder; odourless.

Solubility : Sparingly soluble in *water*; soluble in *alcohol*; slightly soluble in *solvent ether*.

Standards : Salbutamol is 1-(4-hydroxy-3-hydroxymethylphenyl)-2-*tert*-butylaminoethanol. It contains not less than 98.0 per cent and not more than the equivalent of 101.0 per cent of $C_{13}H_{21}NO_3$, calculated with reference to the dried substance.

Identification : (A) The light absorption, in the range 230 to 350 nm, of a layer of a 0.008 per cent w/v solution in *0.1N hydrochloric acid* exhibits a maximum only at 276 nm; *extinction* at 276 nm, about 0.56, Appendix 5.15A.

(B) Complies with **Identification** tests (A) and (B) described under Salbutamol Sulphate.

(C) It melts at about 156°, Appendix 5.11.

Related substances : Carry out the test described under Salbutamol Sulphate, applying separately to the plate 10 µl of each of the two solutions in *methyl alcohol* containing (1) 2.0 per cent w/v of the substance being examined and (2) 0.010 per cent w/v of *1-(4-hydroxy-3-methylphenyl)-2-(tert-butylamino) ethanol R.S.* Any spot in the chromatogram obtained with solution (1), other than the principal spot, is not more intense than the spot in the chromatogram obtained with solution (2).

Boron : Complies with the test described under Salbutamol Sulphate.

Sulphated ash : Not more than 0.1 per cent, Appendix 3.2.7.

Loss on drying : Not more than 0.5 per cent, determined on 1.0 g, by drying 'in vacuo' at 60°, Appendix 5.8.

Assay : Weigh accurately about 0.4 g and dissolve in 50 ml of *glacial acetic acid* by warming, if necessary. Cool, protecting from moisture, and titrate with *0.1N perchloric acid*, using *crystal violet solution* as indicator. Perform a blank determination and make any necessary correction. Each ml of *0.1N perchloric acid* is equivalent to 0.02393 g of $C_{13}H_{21}NO_3$.

Storage : Store in well-closed, light-resistant containers.

Salbutamol Inhaler

Salbutamol Inhalation Aerosol

Category : Bronchodilator (beta-adrenoceptor stimulant).

Dose : For chronic bronchial asthma or as prophylactic, 2 inhalations of 100 µg, 3 or 4 times daily.

For the relief of acute bronchospasm, 1 or 2 inhalations of 100 µg as a single dose when required, upto a maximum of 8 inhalations in twenty-four hours.

Usual strength : 100 µg in each metered dose.

Standards : Salbutamol Inhaler is a susppension of microfine Salbutamol in a suitable mixture of aerosol propellants. It may contain a surfactant, stabilising agents and other pharmaceutical aids. It is packed in a pressurised container fitted with a special metered-dose valve. It contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of Salbutamol $C_{13}H_{21}NO_3$, and it delivers not less than 75.0 per cent and not more than 125.0 per cent of the stated dose per inhalation of $C_{13}H_{21}NO_3$ through an oral inhalation actuator.

Identification : (A) Remove the actuator, shake the container and place it in an inverted position in a small beaker containing 10 ml of *ethyl alcohol.* Deliver 20 sprays under the surface of the solvent, actuating the valve by pressing the tip against the bottom of the beaker. To 1 ml of the solution add 1 ml of a 0.04 per cent w/v solution of *2,6-dichloroquinone chlorimide* in *ethyl alcohol* and 0.1 ml of *dilute ammonia solution;* a bluish-green colour is produced.

(B) Carry out the method for *thin-layer chromatography,* Appendix 5.4.3, using *silica gel G* as the coating substance and a mixture of 100 volumes of *methyl alcohol* and 1.5 volumes of *strong ammonia solution* as the mobile phase. Apply separately to the plate 10 µl of each of the following two solutions. For solution (1) remove the actuator, shake the container well and place it in an inverted position in a small beaker containing 2 ml of *methyl alcohol (80 per cent v/v).* Deliver 40 sprays under the surface of the liquid and use the resulting solution. Solution (2) is a 0.2 per cent w/v solution of *Salbutamol R.S.* in *methyl alcohol (80 per cent v/v).* After removal of the plate allow it to dry in air until the odour of solvent is not detectable and spray with a 0.1 per cent w/v solution of *potassium permanganate.* The principal spot in the chromatogram obtained with solution (1) corresponds to that in the *chromatogram* obtained with solution (2).

Unit spray content : *Apparatus*—A sampling beaker consisting of 150 ml glass beaker in which a stainless steel base plate is placed to facilitate the discharge of the aerosol. The base plate has three legs and a central, circular indentation with a hole approximately 1.5 mm in diameter. The arrangement should prevent particle entrapment and side-of-stem leakage during the delivery of the sample.

Method—Remove the actuator from the pressurised container and remove any attached labels from both the container and the actuator. Wash the actuator with *methyl alcohol* and dry it in a current of nitrogen. Wash the outside of the container and the stem of the valve with *methyl alcohol.* Place 100 ml of *ethyl alcohol* in the sampling beaker, shake the container well and then place it in an inverted position over the base plate. Actuate the valve, discharging the aerosol through the hole in the centre of the base plate. Repeat this procedure a further nine times at intervals of not less than 15 seconds and swirling the contents of the beaker after each spray. Remove the container and rinse the outside of the container and valve stem with *ethyl alcohol* and collect the washings in the beaker. Dilute the combined solution and washings to 200.0 ml with *ethyl alcohol.*

Transfer 20.0 ml of the resulting solution to a separating funnel, add 180 ml of *water* and in the following order, 4 ml of a 5 per cent w/v solution of *sodium bicarbonate,* 4 ml of *N,N-dimethyl-p-phenylenediamine sulphate solution* and 4 ml of a freshly prepared 8 per cent w/v solution of *potassium ferricyanide.* Mix, allow to stand for fifteen minutes in subdued light and extract with two quantities, each of 10 ml, of *chloroform.* Filter the extracts through a cotton-wool plug, dilute to 25.0 ml with *chloroform* and measure the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 650 nm, Appendix 5.15A. Calculate the content of $C_{13}H_{21}NO_3$ from the *extinction* obtained by repeating the operation using a suitable quantity of a 0.001 per cent w/v solution of *Salbutamol R.S.* in *ethyl alcohol.* Calculate the total quantity of $C_{13}H_{21}NO_3$ delivered by the ten actuations of the valve and divide this quantity by ten to obatin the average quantity (x) of salbutamol delivered by one spray from the metered-dose valve. Fit the washed and dried actuator to the container and actuate the valve ten times at intervals of not less 15 seconds. Remove the actuator carefully from the container and immerse it in 40 ml of *ethyl alcohol,* in a small beaker. Swirl the contents, remove the actuator, wash it with small quantities of *ethyl alcohol* and dilute the combined solution and washings to 50.0 ml of *ethyl alcohol.* Transfer 20.0 ml of the resulting solution to a separating funnel and repeat the operation beginning at the words"...add 180 ml of *water...*".Calculate the total quantity of $C_{13}H_{21}NO_3$deposited in the actuator and divide this quantity by 10 to obtain the average quantity of salbutamol (y) deposited in the actuator by one spray of the metered-dose valve. Calculate the unit spray contents from the expression x – y.

Particle size — Prime the valve by alternately shaking and firming it several times through the actuator, and then actuate one measured spray onto a clean dry, microscope slide held 5 cm from the end of the actuator, perpendicular to the direction of the spray. Add 1 ml of *carbon tetrachloride* carefully near the spot where the spray has impinged on the slide and drain after two or three seconds with minimum tilting of the slide. Allow to dry and examine under a microscope, equipped with a calibrated occular micrometer using 450 x magnification. Focus on the particles of 25 fields of view near the centre of the test specimen pattern, and note the size of the great majority of individual particles; they are not more than 5 µm in diameter. Record the number and size of all individual particles (not agglomerates) more than 10 µm in length measured along the longest axis. Not more than 10 such particles are observed and no individual particle exceeds 20 µm in length.

Other requirements : Complies with the requirements stated under Aerosols.

Assay : Remove the label from the container using *methyl alcohol,* if necessary. Place the container in a plastic bag, cool to at least –20° in a refrigerator and then carefully pierce a small hole in the shoulder of the container. Allow the propellants to evaporate (about 3 hours) and remove the top. Wash the top and valve of the opened can with *ethyl alcohol* and collect the washings in a 200 ml volumetric flask. Remove the valve cap and again wash with *ethyl alcohol*. Transfer the contents of the container quantitatively to the volumetric flask. Wash the container thoroughly with *ethyl alcohol,* dilute to 200.0 ml with *ethyl alcohol* and mix well. Dilute 10.0 ml to 200.0 ml with *ethyl alcohol* and mix. Carry out the procedure described under the test for **unit spray content** beginning at the words "Transfer 20.0 ml ...". Calculate the content of salbutamol, $C_{13}H_{21}NO_3$ per container.

Storage : Store in small, non-reactive, light-resistant metal aerosol containers with metered-dose valves and provided with oral inhalation actuators. Store in a cool place, protected from frost. Empty containers must also be protected from heat and direct sunlight.

Lebelling : The label on the container states (1) the number of metered doses available from the container; (2) the amount of active ingredient in the container; (3) the amount of active ingredients delivered per inhalation; (4) that the container should be shaken before each use; (5) that it is dangerous to exceed the recommended dose; (6) a warning that the container is pressurised and must be kept away from heat and direct sunlight and must not be punctured, broken or incinerated even when apparently empty; (7) the warning "keep out of reach of children".

Salbutamol Injection

Salbutamol Sulphate Injection

Category : Bronchodilator (beta-adrenoceptor stimulant).

Dose : By slow intravenous injection, the equivalent of 0.25 mg of salbutamol or by intravenous infusion, the equivalent of 3 to 20 µg of salbutamol per minute.

Usual strengths : The equivalent of 0.25 mg of salbutamol in 1 ml; the equivalent of 0.5 mg of salbutamol in 1 ml.

The equivalent of 5 mg of salbutamol in 5 ml (for intravenous infusion).

Standards : Salbutamol Injection is a sterile solution of Salbutamol Sulphate in Water for Injection containing suitable stabilising agents. The solution is filled in containers in which the air is replaced by nitrogen or any other suitable inert gas. It contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of salbutamol, $C_{13}H_{21}NO_3$.

Description : Clear, colourless or pale straw coloured solution.

Identification : (A) Dilute a volume of the injection with sufficient *0.1 N hydrochloric acid* to produce a solution containing the equivalent of 0.004 per cent w/v of salbutamol; the light absorption of the resulting solution, in the range 230 to 350 nm, exhibits a maximum only at 276 nm, Appendix 5.15A.

(B) Dilute a volume equivalent to 0.5 mg of salbutamol to 50 ml with *water*, add 2 ml of *dilute ammonia solution,* 1 ml of a 3 per cent w/v solution of *4-aminophenazone,* 10 ml of a 2 per cent w/v solution of *potassium ferricyanide* and 10 ml of *chloroform.* Shake and allow to separate; the chloroform layer becomes orange-red in colour.

pH : Between 3.4 and 5.0, Appendix 5.10.

Other requirements : Complies with the requirements stated under Injections.

Assay : Dilute a volume equivalent to 0.15 mg of salbutamol with sufficient *water* to produce 80 ml, add 4 ml of a 5 per cent w/v solution of *sodium bicarbonate,* 4 ml of *N N-dimethyl-p-phenylenediamine sulphate solution* and 4 ml of a freshly prepared 8 per cent w/v solution of *potassium ferricyanide.* Mix, allow to stand for fifteen minutes, protected from light. Extract with two quantities, each of 10 ml of *chloroform.* Filter the extracts through a cotton wool plug and dilute to 25.0 ml with *chloroform.* Measure the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 605 nm, Appendix 5.15A. Calculate the contents of $C_{13}H_{21}NO_3$ from the *extinction* obtained by repeating the operation using 10.0 ml of a 0.0018 per cent w/v solution of *salbutamol sulphate R.S.*, and from the declared content of $C_{13}H_{21}NO_3$, in the *salbutamol sulphate R.S.*

Storage : Store in single-dose, light-resistant containers in which the air has been replaced by nitrogen or other inert gas.

Labelling : The label on the container states the strength in terms of the equivalent amount of salbutamol in a suitable dose-volume.

108832

Spironolactone Tablets

Category : Diuretic (aldosterone antagonist).

Dose : Spironolactone, 0.1 to 0.2 g daily, in divided doses.

Usual strengths : 25 mg; 100 mg.

Standards : Spironolactone Tablets contain not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Spironolactone, $C_{24}H_{32}O_4S$. The tablets may contain added flavouring agents.

Identification : (A) Extract a quantity of the powdered tablets equivalent to 125 mg of Spironolactone with two quantities, each of 10 ml, of *chloroform,* decant, filter, evaporate the combined filtrates to dryness, and dissolve the residue in 2.5 ml of *chloroform.* The *infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *spironolactone R.S.*, Appendix 5.15B.

(B) Extract a quantity of the powdered tablets equivalent to 10 mg of Spironolactone with 5 ml of *chloroform,* filter, and evaporate the filtrate to dryness. The residue complies with **Identification,** tests (B) and (C) described under Spironolactone.

Disintegration : Maximum time, thirty minutes, Appendix 5.6.1.

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 25 mg of Spironolactone, add 100 ml of *methyl alcohol* and heat just to boiling, swirling at frequent intervals. Cool and add sufficient *methyl alcohol* to produce 250.0 ml. Dilute 10.0 ml to 100.0 ml with *methyl alcohol* and measure the *extinction* of the resulting solution at the maximum at about 238 nm, Appendix 5.15A. Calculate the content of $C_{24}H_{32}O_4S$, taking 470 as the value of E (1 per cent, 1 cm) at the maximum at about 238 nm.

Storage : Store in tightly-closed, light-resistant containers.

Trifluoperazine Tablets

Trifluoperazine Hydrochloride Tablets

Category : Antipsychotic (tranquillizer); antiemetic.

Dose : Trifluoperazine Hydrochloride. In psychiatric states, the equivalent of 2 to 30 mg of trifluoperazine daily, in divided doses; as antiemetic, the equivalent of 1 to 6 mg of trifluoperazine daily.

Usual strengths : 1 mg; 5 mg.

Standards : Trifluoperazine Tablets contain an amount of Trifluoperazine Hydrochloride equivalent to not less than 92.5 per cent and not more than 107.5 per cent of the stated amount of trifluoperazine, $C_{21}H_{24}F_3N_3S$. The tablets are sugar-coated.

Identification : (A) Shake a quantity of the powdered tablets equivalent to 20 mg of trifluoperazine with 30 ml of *N hydrochloric acid* for ten minutes, filter, make the filtrate alkaline to *litmus paper* with *sodium hydroxide solution* and extract with two quantities, each of 20 ml, of *light petroleum (boiling range, 60° to 80°)*. Combine the extracts, wash with 10 ml of *water*, shake with 5 g of *anhydrous sodium sulphate*, filter and evaporate the filtrate carefully to dryness. The *infra-red absorption spectrum* of the residue exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to, those in the spectrum of *trifluoperazine R.S.*, treated in a similar manner, Appendix 5.15B.

(B) Extract a quantity of the powdered tablets equivalent to 5 mg of trifluoperazine with 5 ml of *acetone*, filter, and evaporate the filtrate to dryness. Add 2 ml of *sulphuric acid* to the residue and allow to stand for five minutes; an orange colour is produced.

Uniformity of content : Protect the solutions from light throughout the test.

Crush one tablet and transfer to a 100 ml volumetric flask with the aid of 50 ml of a mixture of 1 volume of *hydrochloric acid* and 19 volumes of *water*. Shake well, dilute to volume with the same mixture, mix and filter, rejecting the first 10 ml of the filtrate. Dilute, if necessary, a suitable volume of the filtrate with the same mixture to produce a solution containing 0.001 per cent w/v of trifluoperazine. Measure the *extinction* of a 1-cm layer of the filtrate or the resulting diluted solution at the maximum at about 256 nm, Appendix 5.15A. Calculate the content of $C_{21}H_{24}F_3N_3S$, taking 743 as the value of E (1 per cent, 1 cm) at the maximum at about 256 nm.

Repeat the operation with a further 9 tablets and calculate the average content of the 10 tablets. The content of each tablet is between 90 and 110 per cent of the average except that for one tablet the content may be between 85 and 115 per cent of the average.

Other requirements : Comply with the requirements stated under Tablets.

Assay : Protect the solution from light throughout the assay.

Weigh and powder 20 tablets. Weigh accurately an amount of the powder equivalent to 5 mg of trifluoperazine and shake for fifteen minutes with 400 ml of a mixture of one volume of *hydrochloric acid* and 19 volumes of *water*. Dilute to 500.0 ml with the same mixture, mix, and filter, rejecting the first few ml of the filtrate. Measure the *extinction* of a 1-cm layer of the filtrate at the maximum at about 256 nm, Appendix 5.15A. Calculate the content of $C_{21}H_{24}F_3N_3S$, taking 743 as the value of E (1 per cent, 1 cm) at the maximum at about 256 nm.

Storage : Store in tightly-closed, light-resistant containers.

Labelling : The label on the container states the quantity of the active ingredient in terms of the equivalent amount of trifluoperazine.

Triflupromazine Tablets

Triflupromazine Hydrochloride Tablets,
Fluopromazine Tablets

Category : Antipsychotic (tranquillizer); antiemetic.

Dose : Triflupromazine. In psychiatric states, initial dose 100 to 150 mg daily; maintenance, 30 to 150 mg daily, in divided doses; as an antiemetic, 20 to 30 mg daily.

Usual strength :10 mg; 25 mg.

Standards : Triflupromazine Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of Triflupromazine Hydrochloride, $C_{18}H_{19}F_3N_2S$, HCl.

Identification : Shake a quantity of the powdered tablets equivalent to 50 mg of Triflupromazine Hydrochloride with 20 ml of *acetone*, filter, and evaporate the filtrate to dryness. The residue complies with the following tests.

(A) The *infra-red absorption spectrum* exhibits maxima which are only at the same wavelengths as, and have similar relative intensities to those in the spectrum of *triflupromazine hydrochloride R.S.*, Appendix 5.15B.

(B) The light absorption, in the range 230 to 350 nm, of 1-cm layer of a 0.001 per cent w/v solution in *0.01N hydrochloric acid* exhibits a miximum at about 305 nm, Appendix 5.15A.

(C) A solution (1 in 10) gives the reactions of *chlorides,* Appendix 3.1.

Uniformity of content (for 10 mg tablets only): Crush one tablet and transfer to a 100 ml volumetric flask with the aid of a mixture of 1 volume of *hydrochloric acid* and 19 volumes of *water*. Shake well, dilute to volume with the same mixture, mix and filter, rejecting the first 10 ml of the filtrate. Dilute 10.0 ml of the filtrate to 100.0 ml with *0.01N hydrochloric acid.* Measure the *extinction* of a 1-cm layer of the resulting solution at the maximum at about 255 nm, Appendix 5.15A. Calculate the content of $C_{18}H_{19}F_3N_2S$, HCl, taking 700 as the value of E (1 per cent, 1 cm) at the maximum at about 255 nm.

Repeat the operation with a further 9 tablets and calculate the average content of the 10 tablets. The content of each tablet is between 90 and 110 per cent of the average except that for one tablet the content may be between 85 and 115 per cent of the average.

Other requirements : Comply with the requirements stated under Tablets.

Assay : Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 10 mg of Triflupromazine Hydrochloride and shake for fifteen minutes with a mixture of one volume of *hydrochloric acid* and 19 volumes of *water*. Dilute to 1000.0 ml with the same mixture, mix and filter, rejecting the first few ml of the filtrate. Measure the *extinction* of a 1-cm layer of the filtrate at the maximum at about 255 nm, Appendix 5.15A. Calculate the content of $C_{18}H_{19}F_3N_2S$, HCl, taking 700 as the value of E(1 per cent, 1 cm) at the maximum at about 255 nm.

Storage : Store in well-closed, light-resistant containers.

Typhoid Paratyphoid A Vaccine

Category : Active immunising agent.

Dose : Prophylactic, by subcutaneous injection, 0.5 ml as initial dose; second dose of 0.5 ml after an interval of four to six weeks.

Standards : Typhoid Paratyphoid A vaccine is a sterile suspension prepared from one or more smooth strains of *Salmonella typhi* and *Salmonella paratyphi.* A having a full complement of O,H and Vi antigens in *S. typhi* strain and O and H in *S. paratyphi* A strain. The bacteria are killed by heat or by a bactericide such as phenol or formaldehyhde or by a chemical such as acetone. In case of fluid vaccine it contains a suitable pereservative.

The vaccine for adults contains 1000 million bacteria of *S. typhi* and 500 million bacteria of *S. paratyphi* A per ml. The vaccine for children contains 333 million bacteria of *S. typhi* and 167 million bacteria of *S. paratyphi* A per ml.

Description : White or creamy turbid liquid free from clumps.

Identification : It is identified by specific agglutination, Appendix 2.42.

pH : Between 6.0 and 7.4, Appendix 5.10.

Sterility : Complies with the *tests for sterility* Appendix 4.6.

Undue toxicity : Complies with the *tests for undue toxicity for vaccines and sera,* Appendix 2.37.2.

Phenol (if present) : Not more than 0.5 per cent w/v Appendix 3.3.9.

Storage : Store at a temperature between 2° and 8°. The vaccine must not be frozen.

Labelling : The label on the container states (1) The number of bacteria in each ml and dose schedule; (2) the storage conditions; (3) the date after which the contents are not intended to be used; (4) "not to be frozen"; (5) "Shake well before use"; and (6) the name and proportion of any added preservative.

Typhoid Vaccine (for Children)

Category : Active immunising agent.

Dose : Prophylactic, by subcutaneous injection, 0.5 ml as initial dose; second dose of 0.5 ml after an interval of four to six weeks.

Standards : Typhoid Vaccine (for Children) is a sterile suspension prepared from one or more smooth strains of *Salmonella typhi* having a full complement of O,H and Vi antigens. The bacteria are killed by heat or by a bactericide such as phenol or formaldehyde, or by a chemical such as acetone. The vaccine contains a suitable preservative.

The vaccine contains 333 million bacteria of *S.typhi* per ml.

Description : White or creamy turbid liquid free from clumps.

Identification : It is identified by specific agglutination, Appendix 2.42.

pH : Between 6.0 and 7.4, Appendix 5.10.

Sterility : Complies with the *tests for sterility,* Appendix 4.6.

Undue toxicity : Complies with the *test for undue toxicity for vaccines and sera,* Appendix 2.37.2.

Phenol (if present) : Not more than 0.5 per cent w/v, Appendix 3.3.9.

Storage : Store at a temperature between 2° and 8°. The vaccine must not be frozen.

Labelling : The label on the container states (1) the number of bacteria in each ml and dose schedule; (2) the storage conditions; (3) the date after which the contents are not intended to be used; (4) the name and proportion of any added preservative; (5) "Not to be frozen", and (6) "Shake well before use".

Appendices

Contents of Appendices

Page

Appendix 1 APPARATUS FOR TESTS AND ASSAYS .. A-5

1.2 Sieves .. A-5

Appendix 2 BIOLOGICAL TESTS AND ASSAYS .. A-5

2.24 Biological Assay of Rabies Vaccine .. A-5

Appendix 3 CHEMICAL TESTS AND ASSAYS .. A-5

3.1 Identification Reactions .. A-5
3.2 Limit Tests .. A-5
3.2.1 Limit Test for Arsenic .. A-5

Appendix 4 MICROBIOLOGICIAL TESTS AND ASSAYS .. A-6

4.1 Microbiological Assay of Antibiotics .. A-6
4.2 Assay of Calcium Pantothenate .. A-6
4.5 Microbial Limit Tests .. A-6
4.6 Tests for Sterility .. A-7
4.8 Antimicrobial Preservative-Effectiveness .. A-7

Appendix 5 PHYSICAL TESTS AND DETERMINATIONS .. A-9

5.6 Disintegration Test .. A-9
5.6.1 Disintegration Test for Tablets .. A-9
5.7 Dissolution Test for Tablets and Capsules .. A-9

Appendix 6 GENERAL INFORMATION ..

Appendix 7 REAGENTS AND SOLUTIONS .. A-9

7.1 Buffer Solution .. A-9
7.4 General Reagents .. A-9

APPENDIX-1

1. Apparatus for Tests and Assays

Page A-7

1.2 SIEVES

In the Table, under Nominal mesh aperture size and Tolerance average aperture size,
For 'mm'
read 'µm'

APPENDIX-2

2. Biological Tests and Assays

Page A-37

2.24 BIOLOGICAL ASSAY OF RABIES VACCINE

(4) Determination of potency of the vaccine—line 7
For '0.03 ml'
read '0.5 ml'

2.42 SPECIFIC AGGLUTINATION TEST FOR IDENTITY OF TYPHOID AND TYPHOID PARATYPHOID A VACCINES

The identity test on a batch of typhoid and typhoid paratyphoid A vaccines is carried out by *in-vitro* method.

For the test, the organisms are identified by specific agglutination with factor sera against somatic (0:9) flagellar (H:d) and Vi antigens of *S.typhi* for monovalent vaccine and *S.paratyphi* A(0:2; H:9) also for bivalent vaccine. The test is performed by the slide agglutination method.

Method : Centrifuge 1-2 ml at 2000 rpm for 7-10 minutes. Discard the supernatant, add a few drops of *saline solution* and make an uniform suspension. Perform a slide agglutination test with this suspension using factor sera against somatic, flagellar and Vi antigens for *S. typhi* and somatic and flagellar antigens for *S.paratyphi A.* A positive agglutination with all the antigens employed confirms the identity of Typhoid Paratyphoid A Vaccine, while a positive agglutination with factor sera for antigens of *S.typhi* only and not with *S.paratyphi A* confirms the identity of Typhoid Vaccine.

APPENDIX-3

3. Chemical Tests and Assays

Page A-53

3.1 IDENTIFICATION REACTIONS

After the test for **'Salicylates'** add the following:

Silicates

In a lead or platinum crucible mix, by means of a copper wire to give a thin slurry, the prescribed quantity of the substance being examined, with 10 mg of *sodium fluoride* and a few drops of *sulphuric acid.* Cover the crucible with a thin transparent plate of plastic under which a drop of water is suspended and warm gently; within a short time a white ring is formed around the drop of water.

3.2 LIMIT TESTS

3.2.1 Limit Test for Arsenic

Page A-60

Zinc sulphate—Line 1
For '10 g'
read '1 g'

3.2.5 Limit Test for Iron

Page A-62

Standard iron solution—Line 2
For '10 ml'
read '100 ml'

APPENDIX 4

4. Microbiological Tests and Assays

Page A-89

4.1 MICROBIOLOGICAL ASSAY OF ANTIBIOTICS

TABLE 1, Under column No. 2, Line 2
For 'Ampicillin'
read 'Ampicillin trihydrate'

Page A-92

TABLE 4, under Test Doses
For 'Media concentration'
read 'Median concentration'

Page A-92

TABLE 4, under Further diluent, Lines 1 and 2
For 'Dimethyl Sulphoxide'
read 'Dimethylformamide'

Page A-94

TABLE 4, under ATCC@ No.—Last line
For '6538P'
read '29737'

Page A-96

TABLE 5, under Medium used for, under Roux Bottle, Line 2
For 'A' read 'A*'

TABLE 5, under Incubation period for, under Roux Bottle, Lines 1, 2 and 3
For '1 week' read '5 days'

TABLE 5—Add the following :
Staphylococcus aureus 6538P 1 A A 24 hrs 24 hrs 32-35 1 :20 1 week

Page A-97

Estimation of potency

For "$H = \frac{3c + 2d + c - a}{5}$"

read "$H = \frac{3e + 2d + c - a}{5}$"

Page A-98

Estimation of potency

For “$H = \dfrac{3a + 2d + c - a}{5}$„

read “$H = \dfrac{3e + 2d + c - a}{5}$„

B. TURBIDIMETRIC OR TUBE ASSAY METHOD—Para 2, Line 3

For ‘Standard Preparation of the antibiotic’

read ‘Standard Preparation of the antibiotic (Table 4) and increasing stepwise in the ratio 4 : 5’

4.2 ASSAY OF CALCIUM PANTOTHENATE

Page A-99

Stock culture of organism—Line 10

For ‘*Lactobacillus arabinosus (Lactobacillus plantarum)*’

read ‘*Lactobacillus plantarum ATTC 8014* (formerly known as *Lactobacillus arabinosus 17-5)*’

4.5 MICROBIAL LIMIT TESTS

Page A-102

Deoxycholate citrate agar

For ‘Deoxycholate’

read ‘Desoxycholate’

For ‘Sodium deoxycholate’

read ‘Sodium desoxycholate’

MacConkey’s broth—Line 5

For ‘Bromocresol purple solution’

read ‘Bromocresol purple’

For ‘10 ml’

read ‘0.01 g’

Page A-103

Tetrathionate broth

Add the following:

Do not heat after the iodine has been added. The medium containing iodine should be used on the day it is prepared. The base medium without iodine may be stored indefinitely after sterilisation.

Triple sugar iron agar—Line 11

For ‘13.0 g’

read ‘12.0 g’

Page A-104

(3) **Salmonellae** -Para 2, Line 2

For ‘*salenite*’

read ‘selenite’

Page A-105

Secondary test—Para, 2, Line 3

For ‘*Salmonellae*’

read ‘*Salmonella*’

4.6 TESTS FOR STERILITY

Page A-107

I. Fluid thioglycollate medium—Line 4

For ‘Resazurin (1.10% fresh solution)’

read ‘Resazurin (0.10% fresh solution)’

Lines 16 to 23

After ‘add the resazurin solution’

change the statement to:
'Distribute into suitable vessels which provide a ratio of surface to depth of medium such that not more than the upper half of the medium has undergone a colour change, indicative of oxygen uptake at the end of the incubating period. Sterilise by autoclaving for 13 to 20 minutes at 121° (15 lbs/psi, approx. 1.0 kg/cm²). Cool promptly to 25° and store at 20° to 30°, avoiding excess of light. If more than the upper one-third has acquired a pink colour, the medium may be restored *once* by re-heating in a water-bath until the pink colour disappears and cooling rapidly. When ready for use, not more than the upper one-tenth of the medium should have a pink colour.'

Page A-107 *II. Alternative thioglycollate medium*—Line 7
For 'Dextrose ($C_6H_{12}O_6H_2O$)'
read 'Dextrose ($C_6H_{12}O_6\ H_2O$)'

Medium for fungi and aerobic bacteria
Soybean-casein digest medium—Line 5
For 'Dextrose ($C_6H_{12}O_6\ H_2O$)'
read 'Dextrose ($C_6H_{12}O_6\ H_2O$)'

4.8 ANTIMICROBIAL PRESERVATIVE-EFFECTIVENESS

The function of a preservative in pharmaceutical preparation is to protect the patient from microbial contamination and to maintain potency and stability. It is used in those products that may support the growth of microbial contaminants in the absence of preservative. Preservatives should not be used solely to reduce the viable count of microorganism as a substitute for Good manufacturing practice. The concentration of antimicrobial agent in Pharmaceutical Preparations should be considerably below the concentration of the antimicrobial agent that may be toxic to human beings.

The effectiveness of added antimicrobial agent in multi-dose parenteral, otic, nasal and opthalmic preparations made with aqueous bases or vehicles can be demonstrated by the following tests:

Test Organisms :
The following test organisms are used in the test:
Candida albicans ATCC 10231
Aspergillus niger ATCC 16404
Escherichia coli ATCC 8739
Pseudomonas aeruginosa ATCC 9027
Staphylococcus aureus ATCC 6538

Medium : For the initial cultivation of the test organism, use Soybean-casein Digest Agar Medium or any other medium not less nutritive than the said medium.

Preparation of inoculum : From a recently grown stock culture of each of the test organisms, subculture on the surface of a suitable volume of above stated medium. Incubate the bacterial cultures at 30° to 35°C for 18 to 24 hrs, and incubate the cultures of *C. albicans* and *A. niger* at 20° to 25°C for 48 hrs and 7 days respectively.

Using sterile 0.9% saline, harvest the bacteria and *C. albicans* cultures and dilute suitably with sterile 0.9% saline to bring the count to about

1 x 10^8 per ml. Similarly harvest *A. niger* culture with 0.9% saline containing 0.05% polysorbate 80 and adjust the spore count to about 1 x 10^8 per ml with sterile 0.9% saline.

Procedure : Inoculate each original product container or product tube (when original container is not suitable for inoculation with sterile syringe fitted with needle, transfer 20 ml per capped bacteriological tube) with one of the standardised microbial suspension using a ratio equivalent to 0.1 ml of inoculum suspension to 20 ml of product, and mix. Final concentration should be between 1 x 10^5 and 1 x 10^6 microorganisms per ml of product. Determine, the number of viable microorganisms by plate count method in each inoculum suspension and from there calculate the initial concentration of microorganisms per ml of product under test.

Incubate the inoculated containers of tubes at 20° to 25°C, Determine the viable count (by plate count method) at 7, 14, 21 and 28 days subsequent to inoculation. Record also any change observed in appearance.

Interpretation : The preservative is effective in the product examined if (a) the concentrations of viable bacteria are not more than 0.1% of the initial concentrations by the 14th day; (b) the concentrations of viable yeasts and mold remain at or below the initial concentration during the first 14 days; and (c) the concentration of each test microorganism remains at or below these designated levels during the remainder of the 28-days test period.

APPENDIX 5

5. Physical Tests and Determinators

5.6 DISINTEGRATION TEST

5.6.1. Disintegration Test for Tablets

Page A-122

Apparatus—Line 12
For '1.5 mm square'
read '1.6 mm square'

5.7 DISSOLUTION TEST FOR TABLETS AND CAPSULES

Page A-122

Apparatus—Line 7
For '60'
read '160'

APPENDIX 7

7. Reagents and Solutions

7.1 BUFFER SOLUTIONS

B. Other Buffer Solutions

Page A-143

After **Ammonia buffer pH 10.0** insert the following:

Ammonia buffer pH 10.9: Dissolve 67.5 g of *ammonium chloride* in 650 ml of *strong ammonia solution* and dilute with *water* to 1000 ml.

Citro-phosphate buffer, pH 7.6 : Dissolve 0.267 g of *citric acid* and 13.41 g of *sodium phosphate* in sufficient water to produce 200.0 ml.

7.4 GENERAL REAGENTS

Boric Acid Solution : Dissolve 5 g of *boric acid* in a mixture of 20 ml of *water* and 20 ml of *absolute ethanol* and dilute with *absolute ethanol* to 250 ml.

N,N-Dimethyl-p-phenylene diammonium sulphate : $C_8H_{12}N_2, H_2SO_4 = 234.3$
General reagent grade of commerce

N, N-Dimethyl-p-phenylene diammonium sulphate solution : Boil 25 g of *N, N-dimethyl-p-phenylenediammonium* with 600 ml of *ethanol* (90 per cent) under reflux when dissolved, add decolorising *charcoal*, mix well, and filter whilst hot; allow to cool overnight and then in a bath of ice, filter through sintered glass, wash with ice-cold *absolute ethanol* until free from colour, and dry under reduced pressure at room temperature. Dissolve 50 mg of the recrystallised material in sufficient *water* to produce 50 ml.

Isopropyl Ether : $[(CH_3)_2\ CH]_2O = 102.2$
General reagent grade of commerce.
A colourless liquid with a characteristic odour; boiling point, about 68°; weight per ml, about 0.72 g. Di-isopropyl Ether should be protected from light and, for safety, mixed with 0.01 per cent w/v of *hydroquinone* as an antioxidant.

WARNING : It is dangerous to distil or evaporate di-isopropyl ether unless precautions have been taken to remove peroxides.

Nile Blue A : CI 51180; $C_{20}H_{21}N_3O_5S = 415.5$
Complies with the following test :
Light Absorption A 0.0005 per cent w/v solution in *ethanol* (50 per cent) exhibits an absorption maximum at about 640 nm. Gives a blue colour with weakly alkaline solutions and a red colour with strongly alkaline solutions (pH range, 9.0 to 13.0).

Nile Blue A Solution : A 1.0 per cent w/v solution of nile blue A in *anhydrous glacial acetic acid* complies with the following test :

Sensitivity : A solution containing 0.25 ml in 50 ml *anhydrous glacial acetic acid* is blue. Not more than 0.1 ml of 0.1M *perchloric acid vs* is required to change the colour of the solution to blue green.

Nitrate Standard Solution (100 ppm NO_3) : Dilute 10.0 ml of a 0.163 per cent w/v solution of *potassium nitrate* with *water* to 100.0 ml.

Nitrate Standard Solution (2 ppm NO_3) : Dilute 2.0 ml of *nitrate standard solution (100 ppm NO_3)* with *water* to 100.0 ml.

Page A-235

Sulphuric Acid, xN—Line 2
For '54 x ml'
read '27 x ml'

Trinitrophenol Solution : Add 0.5 ml of 5M *sodium hydroxide* to 100 ml of a saturated solution of *2,4,6-trinitrophenol* in water.

Zirconyl Nitrate : Approximately $ZrOCl_2$, $8H_2O$ = 322.3
Use as a grade of commerce supplied especially for fluoride determinations.

Zirconyl Nitrate Solution : Dissolve 0.1g of *Zirconyl nitrate* in a mixture of 60 ml of *hydrochloric acid* and 40 ml of *water*.

Page A-246

7.5 VOLUMETRIC REAGENTS AND SOLUTIONS

Perchloric Acid, 0.1N (in Glacial Acetic Acid)—Line 9
For '100 ml'
read '1000 ml'

Index

Index

A

Absorbent Lint .. 13
Aerosols .. 27
Aerosol, Salbutamol Inhalation .. 56
Albuterol .. 56
Aluminium Hydroxide Gel .. 3
Aluminium Hydroxide Gel, Dried .. 3
Amendments to the Monographs .. 1
Aminoacetic Acid .. 36
Aminocaproic Acid .. 3
Amoxycillin Mixture .. 28
Amoxycillin for Oral Suspension .. 28
Ampicillin Injection .. 3
Anaesthetic ether .. 10
Analgin .. 3
Anhydrous Citric Acid .. 6
Anticoagulant Sodium Citrate Injection .. 3
Anticoagulant Sodium Citrate Solution .. 3
Antimicrobial Preservative Effectiveness .. A-6
Antiserum Snake Venom .. 18
Apparatus for Tests and Assays .. A-3
Appendices .. A-1
Arsenic, Limit Test for .. A-6
Aspirin Tablets, Soluble .. 3
Assay of Calcium Pantothenate .. A-7

B

Beclomethasone Dipropionate .. 29
Benzyl Benzoate .. 3
Benzyl Benzoate Application .. 3
Biological Assay of Rabies Vaccine .. A-5
Biological Tests and Assays .. A-5
Bisacodyl Tablets .. 4
Blood, Whole (Human) .. 4
Boric Acid .. 4
Boric Acid, Solution .. A-10
Buffer Solutions .. A-9

C

Calcium Carbonate .. 4
Calcium Lactate .. 4
Calcium Pantothenate, Assay .. A-5
Calcium Phosphate, Dibasic .. 4
Capsules, Dextropropoxyphene .. 33
Capsules, Dextropropoxyphene Hydrochloride .. 33
Capsules, Doxepin .. 35
Capsules, Doxepin Hydrochloride .. 34
Capsules, Ethosuximide .. 35
Capsules, Propoxyphene, Dextro .. 33
Carbenicillin Injection .. 5
Carbimazole Tablets .. 30
Cellulose, Microcrystalline .. 5
Cephalexin .. 5
Chemical Tests and Assays .. A-5
Chlorides, Limit Test for .. 23
Chlordiazepoxide .. 5
Chlorocresol .. 5
Chloroform .. 5
Chloroquine Phosphate .. 6
Chloroquine Phosphate Tablets .. 6
Cholecalciferol .. 6
Cholera Vaccine .. 6
Citric Acid, Anhydrous .. 6
Citro-phosphate Buffer, pH 7.6 .. A-10
Clonidine Hydrochloride .. 6
Clonidine Hydrochloride Injection .. 30
Clonidine Injection .. 30
Clonidine Tablets .. 7
Clotrimazole .. 31
Cloxacillin Injection .. 7
Cloxacillin Sodium .. 7
Colchicine Tablets .. 32
Cortisol Hemisuccinate .. 40
Cyclophosphamide Tablets .. 7
Cyproheptadine Tablets .. 8

D

Dapsone .. 8
Demethyl Chlortetracycline Hydrochloride .. 8
Deoxycholate Citrate Agar .. A-7
Dextrin .. 32
Dextropropoxyphene Capsules .. 33
Dialysis Fluid, Tetraperitoneal .. 12
Dibasic Calcium Phosphate .. 4
Diloxanide Furoate Tablets .. 8
Diluted, Isosorbide Dinitrate .. 12
Diluted, Pentaerythritol Tetranitrate .. 49
N, N-Dimethyl-p-phenylene diammonium Sulphate Solution .. A-10
Diphenhydramine Hydrochloride .. 8
Diphtheria and Tetanus Vaccine (Adsorbed) .. 8
Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed) .. 9
Disintegration Test .. A-9
Disintegration Test for Tablets .. A-9
Dissolution Test for Capsules and Tablets .. A-9
Doxepin Capsules .. 35
Doxepin Hydrochloride .. 34
Doxepin Hydrochloride Capsules .. 35
Dried Aluminium Hydroxide Gel .. 3

E

Ephedrine Hydrochloride .. 9
Ephedrine Tablets .. 9
Erythromycin .. 9
Erythromycin Estolate .. 10
Erythromycin Estolate Tablets .. 10

Erythromycin Stearate .. 10
Erythromycin Tablets .. 10
Ethambutol Hydrochloride .. 10
Ether, Anaesthetic .. 10
Ethinylestradiol .. 10
Ethinylestradiol Tablets .. 3
Ethosuximide Capsules .. 35
Eucalyptus Oil .. 11

F

Ferrous Gluconate .. 11
Fluid Thioglycollate Medium .. A-7
Flupromazine Tablets .. 58
Frusemide Injection .. 11

G

Gelatin .. 11
General Reagents .. A-10
Gentamicin Injection .. 11
Gentamicin Sulphate .. 11
Glycerin .. 11
Glycine .. 36
Griseofulvin .. 12

H

Hard Paraffin .. 16
Haloperidol .. 37
Haloperidol Tablets .. 38
Halothane .. 39
Hydrochlorothiazide .. 39
Hydrocortisone Acetate .. 12
Hydrocortisone Hemisuccinate .. 40
Hydrocortisone Hydrogen Succinate .. 40
Human Blood, Whole .. 4

I

Identification Reactions .. A-5
Index .. A-1
Inhaler, Salbutamol .. 56
Injections .. 12
Injection, Ampicillin .. 3
Injection, Anticoagulant Sodium Citrate .. 3
Injection, Carbenicillin .. 5
Injection, Clonidine .. 30
Injection, Clonidine Hydrochloride .. 30
Injection, Cloxacillin .. 7
Injection, Frusemide .. 11
Injection, Gentamicin .. 11
Injection, Iodoxyl .. 3
Injection, Isoxsuprine .. 40
Injection, Isoxsuprine Hydrochloride .. 40
Injection, Lignocaine and Adrenline .. 13
Injection, Lignocaine Hydrochloride .. 42
Injection, Metoclopramide .. 44
Injection, Oxytetracycline Hydrochloride .. 15
Injection, Pentazocine .. 51
Injection, Pentazocine Lactate .. 51
Injection, Promethazine .. 54
Injection, Promethazine Hydrochloride .. 54
Injection, Propranolol .. 55
Injection, Propranolol Hydrochloride .. 55
Injection, Salbutamol .. 58
Injection, Salbutamol Sulphate .. 58
Injection, Succinylcholine Chloride .. 21
Injection, Tetracycline .. 22
Intraperitoneal Dialysis Fluid .. 12
Introduction .. xii
Iodoxyl, Injection .. 3
Ipecacuanha .. 3
Iron, Limit Test for .. A-6
Isoniazid .. 12
Isopropyl Ether .. A-10
Isosorbide Dinitrate, Diluted .. A-12
Isoxsuprine Hydrochloride Injection .. 40
Isoxsuprine Hydrochloride Tablets .. 41
Isoxsuprine Injection .. 40
Isoxsuprine Tablets .. 41

L

Lactose .. 13
Legal Notices .. v
Lignocaine and Adrenaline Injection .. 13
Lignocaine Hydrochloride Injection .. 42
Limit Test .. A-6
Limit Test for Arsenic .. A-6
Limit Test for Chlorides .. 23
Limit Test for Iron .. A-6
Limit Test for Microbials .. A-7
Lint, Absorbent .. 13
Lithium Carbonate .. 3

M

Mac Conkey's Broth .. A-7
Mannitol .. 13
Measles Vaccine Live .. 13
Mercaptopurine Tablets .. 42
Metformin Hydrochloride Tablets .. 42
Metformin Tablets .. 42
Methyl Salicylate .. 14
Methyl Dopa .. 14
Metoclopramide Hydrochloride .. 43
Metoclopramide Hydrochloride Injection .. 44
Metoclopramide Injection .. 44
Metoclopramide Tablets .. 45
Metronidazole Benzoate .. 14
Miconazole Nitrate .. 45
Microbial Limit Test .. A-7
Microbiological, Assay of Antibiotics .. A-6
Microbiological Tests and Assays .. A-6
Microcrystalline Cellulose .. 5
Monographs .. 25

N

Naproxen .. 46
Naproxen Tablets .. 47
Nikethamide .. 14
Nile Blue A .. A-10
Nile Blue A Solution .. A-10
Nitrate Standard Solution (100 ppm NO_3) .. A-10
Nitrate Standard Solution (2 ppm NO_3) .. A-10
Nitrazepam .. 47
Nitrazepam Tablets .. 48
Notices .. v

Nystatin .. 15
Nystatin Ointment .. 15
Nystatin Tablets .. 15
Nystatin Vaginal Tablets .. 15

O

Oil, Eucalyptus .. 11
Ointment, Nystatin .. 15
Oral Suspension, Amoxicillin .. 26
Oxygen .. 15
Oxyphenbutazone .. 15
Oxytetracycline .. 15
Oxytetracycline Hydrochloride Injection .. 15

P

Paraffin, Hard .. 16
Patents and Trademarks .. v
Pentaerythritol Tetranitrate, Diluted .. 49
Pentaerythritol Tetranitrate Tablets .. 50
Polio Virus Vaccine .. 53
Pentazocine .. 50
Pentazocine Hydrochloride Tablets .. 52
Pentazocine Injection .. 51
Pentazocine Lactate Injection .. 51
Pentazocine Tablets .. 52
Pepsin .. 16
Perchloric Acid, 0.1N .. A-11
Phenylbutazone .. 16
Phenylbutazone Tablets .. 16
Phthalylsulphathiazole .. 16
Poliomyelitis Vaccine (Oral) .. 17,53
Potassium Iodide .. 17
Powdered Tragacanth .. 22
Prednisolone Acetate .. 17
Prednisolone Tablets .. 17
Preface .. vii
Procaine Penicillin .. 17
Promethazine Hydrochloride Injection .. 54
Promethazine Injection .. 54
Propantheline Bromide Tablets .. 55
Propantheline Tablets .. 55
Propoxyphene Capsules .. 33
Propoxyphene Hydrochloride, Dextro .. 17
Propoxyphene Hydrochloride Dextro, Capsules .. 33
Propranolol Hydrochloride .. 17
Propranolol Hydrochloride Injection .. 55
Propranolol Injection .. 55
Purified Water .. 23

Q

Quiniodochlor .. 17
Quiniodochlor Tablets .. 17

R

Rabies Vaccine .. 18
Rabies Vaccine, Biological Assay .. A-5
Reagents and Solutions .. A-9
Riboflavine .. 18
Riboflavine Phosphate Sodium .. 18
Rifampicin .. 18

S

Salbutamol .. 56
Salbutamol Inhaler .. 56
Salbutamol Inhaler Aerosol .. 56
Salbutamol Injection .. 58
Salbutamol Sulphate .. 18
Salbutamol Sulphate Injection .. 58
Salmonellae, Test for .. A-7
Silicates .. A-5
Snake Venom Antiserum .. 18
Sodium Bicarbonate .. 19
Sodium Carboxymethyl Cellulose .. 19
Sodium Chloride .. 19
Sodium Citrate .. 19
Sodium Citrate Injection, Anticoagulant .. 3
Sodium Citrate Solution, Anticoagulant .. 3
Sodium Hydroxide .. 19
Soluble Aspirin Tablets .. 3
Sorbitol .. 20
Sorbitol Solution .. 18
Specific Agglutination Test .. A-5
Spironolactone Tablets .. 59
Standard Iron Solution .. A-10
Standard Nitrate Solution (100 ppm NO_3) .. A-10
Standard Nitrate Solution (2 ppm NO_3) .. A-10
Starch .. 20
Sterile, Water for Injection .. 23
Sterility, Test for .. A-7
Streptomycin Sulphate .. 20
Succinylcholine Chloride Injection .. 20
Sucrose .. 20
Sulphadimethoxine .. 21
Sulphadimidine Sodium .. 21
Sulphadoxine .. 21
Sulphamethoxazole .. 21
Sulphaphenazole .. 21
Sulphuric Acid, xN .. 21

T

Tablets, Aspirin Soluble .. 3
Tablets, Bisacodyl .. 4
Tablets, Carbimazole .. 30
Tablets, Chloroquine Phosphate .. 6
Tablets, Clonidine .. 7
Tablets, Colchicine .. 32
Tablets, Cyclophosphamide .. 7
Tablets, Cycloheptadine .. 8
Tablets, Diloxamide Furoate .. 8
Tablets, Erythromicine Estolate .. 10
Tablets, Erythromicine .. 10
Tablets, Ethinylestradiol .. 3
Tablets, Flupromazine .. 60
Tablets, Haloperidol .. 38
Tablets, Isoxsuprine .. 38
Tablets, Isoxsuprine Hydrochloride .. 41
Tablets, Mercaptopurine .. 42
Tablets, Metformin .. 42
Tablets, Metformin Hydrochloride .. 42
Tablets, Metoclopramide .. 45
Hydrochloride .. 45
Tablets, Naproxen .. 47
Tablets, Nitrazepam .. 48
Tablets, Nystatin .. 15

Tablets, Nystatin Vaginal .. 15
Tablets, Pentaerythritol .. 50
Tablets, Pentaerythritol Tetranitrate .. 50
Tablets, Pentazocine .. 52
Tablets, Pentazocine Hydrochloride .. 52
Tablets, Phenylbutazone .. 16
Tablets, Prednisolone .. 17
Tablets, Quiniodochlor .. 17
Tablets, Spironolactone .. 59
Tablets, Trifluoperazine .. 59
Tablets, Trifluoperazine Hydrochloride .. 60
Tablets, Triflupromazine .. 60
Tablets, Triflupromazine Hydrochloride .. 60
Test for Salmonellae .. A-7
Test for Special Agglutination .. A-5
Test for Sterility .. A-7
Tetanus Vaccine (Adsorbed) .. 21
Tetracycline .. 21
Tetracycline Eye Ointment .. 22
Tetracycline Injection .. 22
Tetrathionate Broth .. A-7
Thiamine Hydrochloride .. 22
Tragacanth, Powdered .. 22
Triamcinalone .. 22
Trifluoperazine Tablets .. 59
Trifluoperazine Hydrochloride Tablets .. 59
Triflupromazine Tablets .. 60
Triflupromazine Hydrochloride Tablets .. 60
Trimethoprim .. 22
Triple Sugar Iron Agar .. A-7
Trinitrophenol Solution .. A-11
Typhoid Paratyphoid A, Vaccine .. 61
Typhoid Vaccine .. 22
Typhoid Vaccine (for Children) .. 62

V

Vaccine Cholera .. 6
Vaccine, Diphtheria and Tetanus Adsorbed .. 8
Vaccine, Measles Live .. 13
Vaccine, Poliomyelitis (Oral) .. 17, 53
Vaccine Poliovirus (Oral) .. 53
Vaccine, Rabies .. 18
Vaccine, Tetanus (Adsorbed) .. 21
Vaccine, Typhoid .. 22
Vaccine, Typhoid (for Children) .. 62
Vaccine, Typhoid Paratyphoid A .. 61
Vaccine, Yellow Fever .. 23
Vaginal Tablets, Nystatin .. 15
Volumetric Reagents and Solutions .. A-11

W

Water for Injection, Sterile .. 23
Water, Nitrate Free .. 23
Water, Purified .. 23
Whole Human Blood .. 4

Y

Yellow Fever Vaccine .. 23

Z

Zinc Sulphate .. A-6
Zirconyl Nitrate .. A-11
Zirconyl Nitrate Solution .. A-11

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